Virtual reality for research and treatment of psychosis

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VIRTUAL REALITY

FOR RESEARCH AND TREATMENT OF PSYCHOSIS

Virtual reality for research and treatment of psychosis

Roos MCA Pot-Kolder

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Virtual reality for research and treatment of psychosis

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promotoren: prof.dr. M. van der Gaag
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Chapter 1

Introduction and outline of the thesis

Virtual reality

A virtual reality (VR) is a simulated environment generated by a computer (see figure 1.1). Virtual environments are well known from gaming, where you can create a virtual character and go on adventures in a virtual environment. Technically, the term virtual reality could also be applied to two-dimensional programs displayed on a traditional computer monitor, but in this thesis, VR specifically refers to the use of a head mounted display (HMD) presenting the user with immersive 3D environments in a first-person perspective (figure 1.2). The HMD contains two small displays that show slightly

Figure 1.1. Simulated environment generated by a computer.
Source: CleVR.net

Figure 1.2. Head mounted display.

different images to the left and right eye, creating a 3D effect for the user. The HMD is equipped with sensors that track the movement of the user. This information is sent back to the computer and used to update the virtual environment. If the user turns their head to the left, the computer generates the left part of the virtual environment for them to see. This adaptation of the virtual environment happens so fast that it seems instantaneous to the user, giving them a sense of continued presence. Usually, the user can interact with the virtual environment by using a keyboard or controllers.

While the technology of VR has been around for decades, it has now become more affordable, available and user-friendly than before. Immersive VR environments give people a sense of presence, of 'being there', while simultaneously being aware that the virtual environment is not real[1]. While this double awareness is tolerated by most people, some develop cybersickness. Cybersickness is the experience of motion sickness-like symptoms such as nausea while being exposed to a VR environment[2] and it diminishes the sense of presence[3]. Immersive VR makes it possible to bring real-life situations into the therapy or research room by using 3D VR-glasses, in a safe and controlled manner.

VR in psychology

Research on the use of VR in psychology includes work on assessing psychiatric disorders through VR[4], using VR environments to explore working mechanisms of symptoms and VR therapy[5,6]. VR therapy research has been conducted for over two decades[7] and has focused mainly on treating anxiety disorders[5]. Virtual reality exposure therapy produces significant behavior changes in real-life situations[8]. Exposure to feared stimuli and reducing safety behaviors is an essential part of treating anxiety. VR technology allows therapists to expose people to their feared stimuli in VR or 'in virtuo' to help them deal with these stimuli in their daily lives.

VR treatment of social anxiety disorder shows that interactive virtual social environments can enable people to effectively confront their fears about being rejected by other people[9]. A similar approach could be used for people suffering from unfounded anticipation of intentional harm inflicted by other people. Studies have shown that virtual experiences were safe and acceptable for patients suffering from psychosis[10] and for patients assessed with an at risk mental state for developing psychosis[11], opening up possibilities for further research. A more recent review study confirms the safety and acceptability of using virtual reality with people experiencing psychotic symptoms[12]. Their attitude towards virtual reality was positive and they completed the tasks that were given to them[13]. People with paranoid ideation are constantly on the lookout for other people wanting to hurt them[14]. They either avoid social situations or endure them with high levels of stress using situational safety behaviors such as avoiding eye contact and remaining silent[15]. Often, people with paranoid ideation have a history of interpersonal trauma such as

neglect, abuse or bullying; i.e. of being hurt by other people[16]. Traumatic experiences should be discussed with the patient at the start of treatment. When PTSD-classification is met, trauma-focused therapy should be conducted first as this improves both PTSD symptoms and psychotic symptoms[17]. The safety behaviors and avoidance strategies they've adopted prevent them from having any corrective positive or neutral experiences with other people to reduce their paranoid fears[18]. VR therapy using interactive social environments would be a valuable first step in gaining these experiences.

Psychosis and paranoid ideation

Some people are vulnerable to developing psychotic symptoms, in the same way that others are vulnerable to developing anxiety or depression. Psychotic symptoms exist on a continuum across the general population[19]. Many people have psychotic-like experiences, such as hearing your phone ringing when it didn't or thinking that, when you hear people laughing, they are laughing at you. There is a small group of people that experiences many of these psychotic experiences at once. Or they experience them more strongly, for instance hearing voices that others can't hear or thinking the people they hear laughing are plotting to hurt them. If these experiences become too much for a person to bear and start to interfere with their ability to function, we call the symptoms a disorder. The current diagnostical classification manual used in the Netherlands is the DSM-5[20], which defines psychotic disorders according to abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms[21]. A common experience is paranoid ideation, with regular experiences such as mistrust, interpersonal sensitivity and ideas of reference on one end of the continuum, and full persecutory delusions on the other end[22]. Paranoid ideation is exponentially distributed and hierarchically arranged across the human population. Persecutory delusions are reported by 70%[23] to 90%[18] of people diagnosed with a psychotic disorder to some degree. If you fear that other people want to hurt or even kill you, it is an understandable response to avoid social situations. While avoidance helps to feel safe in the short term, it leads to social withdrawal, isolation and loneliness in the long term. We see that people diagnosed with a psychotic disorder spend more time alone than people without a psychotic disorder[24]. Their social networks are generally limited, and many do not have a partner relationship[25]. Unemployment rates are high[26].

Environmental factors in psychosis

Psychology is a relatively young science, and at the cutting edge of interacting biological, social and psychological factors. Social factors have both a developmental influence and

a real-time influence on how we perceive social situations. Experiencing adverse life events during developmental years, such as childhood trauma, is related to an increased risk of developing psychotic disorders[27]. Later in life, stress sensitivity and learned threat anticipation increase chances for a psychotic evaluation of everyday life events and stressors[28]. Social context is thus inextricably bound up with psychotic experiences such as paranoid ideation, and research on mechanisms of paranoid ideation should incorporate social context. Research has shown that when exposed to a social environment, people with persecutory delusions report an increase in levels of anxiety and paranoid ideation[29]. Scientific research in real-life social environments is complicated by the fact that social environments are always changing, and each participant will inevitably encounter different people. VR can present the same social environments and stimuli to multiple subjects, enabling scientific experimentation.

Other studies have used the Experience Sampling Method (ESM) to incorporate social context in their design[30]. With ESM, participants wear technology in their daily life that beeps at random intervals, at which time a brief questionnaire can be answered. But ESM data still poses a challenge, as social contexts are continually changing and there is an interaction effect between the participant and other people. For research purposes, full control and repeatability of social contexts (while still being as realistic as possible) are necessary to better understand the mechanisms of paranoid ideation.

Antipsychotic treatment with medication

According to The National Institute for Health and Care Excellence (NICE) guidelines, treatment of psychotic symptoms consists of antipsychotic medication and added cognitive behavioral therapy for psychosis (CBTp)[31].The NICE guidelines for psychosis and schizophrenia also mention that the patient and the healthcare professional should make the choice for pharmacotherapeutic treatment together. Antipsychotic medication can help reduce psychotic symptoms, but effect sizes are small to moderate[32]. The conditioned social avoidance resulting from paranoid ideation and anxiety does not always improve with antipsychotic medication[18]. The use of antipsychotic medication does not always prevent relapse (27% within one year)[33]. First episode psychosis even has 78% relapses in 24 months[34]. Besides the benefits, there is also a risk of side effects when using antipsychotic medication[35]. Common side effects include motor disturbances like parkinsonism, breast milk production in male, weight gain, decreased sexual libido and dysphoria. Since such side effects can negatively impact quality of life, patients often opt out of using antipsychotic medication, even if it does help in decreasing their psychotic symptoms[36].

CBTp with exposure

Cognitive behavioral therapy for psychosis is the most effective psychotherapy in treating paranoid ideation[37], and the NICE guidelines recommend at least sixteen individual sessions[31]. There is robust evidence for the effects on delusions and hallucinations[38]. Recent research also indicates that CBTp is effective for people who do not use antipsychotic medication[39].

A vast amount of scientific research publications has demonstrated the treatment effect of exposure therapy[40]. Exposure is the core component of any anxiety treatment, including paranoid anxiety. In exposure sessions, people are confronted with feared stimuli to test the accuracy of their expected negative outcome. When they are exposed to the feared stimuli but the expected negative outcome does not occur, they start to develop a more realistic outcome expectancy, and their anxiety drops.

There are several challenges with exposure therapy to which VR could offer solutions. Since VR is not real, the threshold to start exposure therapy is expected to be low. Furthermore, some individuals do not benefit from exposure treatment and others experience a recurrence of fear after treatment. A core mechanism believed to underlie exposure therapy is inhibitory learning[41]. Several exposure optimization strategies are proposed to strengthen the effect of inhibitory learning[41]. VR is expected to contribute to several of these, because of the extended level of control over the virtual exposure conditions. Two enhancement possibilities that VR offers are 'variability' and 'multiple contexts'. By varying the stimuli and contexts in which exposure takes place, the retrievability of newly learned information increases. Recurrence of fear after treatment is expected to decline. Furthermore, VR can be used to maximize expectancy violation. Stimuli can be added during exposure and negative outcome scenarios can be created, for instance, a virtual social rejection scenario in which a person can experience that, while social rejection is an unpleasant experience, they are able to handle it and do not experience the anticipated negative consequences.

Virtual reality-based cognitive behavioral therapy (VR-CBT)

Using VR to enhance CBT for people suffering from paranoid ideation has several advantages. Many of these patients see it as a more acceptable start of therapy because it is not real. An added advantage of in virtuo is that exercises can take place in the privacy of the therapy room, with the full support of the attendant therapist. During in virtuo exercises in the therapy room, all thoughts, feelings and behaviors can be discussed in real-time. Another advantage of VR is the opportunity for the therapist to use positive affirmation when the patient is taking important steps and performing difficult tasks. At the same time, it can sometimes be useful to correct unhelpful behavior.

Another important advantage of in virtuo therapy is that learning environments can be personalized and controlled by the therapist. Interactive environments can be created based on the individual paranoid expectations of the patient. Finally, the exercises can be repeated as many times as patient and therapist want. The virtual people will not react any differently the fourth or even twentieth time a patient does an exercise.

The core of VR-CBT is reducing safety behaviors while actively testing harm expectancies during behavioral experiments. Safety behaviors get in the way of having corrective experiences. A patient who feels safe because they do not make eye contact with other people will never learn that they are still safe when they do make eye contact with people. During therapy, patients are actively testing their paranoid expectancies. They expose themselves to virtual social situations while reducing their safety behaviors such as avoiding eye contact, escaping from the situation, showing obedience to avatars, seeking aid from others or turning to aggression. While being exposed to the social situation, they actively test harm expectancies such as: 'If I make eye contact with other people, they will react aggressively towards me'. The outcome of this particular behavioral experiment will likely be: 'If I make eye contact with people, they will just look away after a few seconds and do nothing'.

In addition to experiencing corrective neutral or positive social situations, VR can also be used to test harm expectancies in negative social situations. This usually takes place in a later stage of the therapy, and never without consent. For example, many patients fear that other people will think of them as being 'weird'. That also raises the interesting question of what 'normal' even is and why a person would want to strive for it. Neutral or positive interpersonal experiences are what most everyday social interactions look like. But what if you do encounter an unpleasant person? A bully? What if someday, somebody *will* call you weird? VR offers an opportunity to test this situation. The patient can even experiment with different healthy reactions to being called 'weird'. What patients learn through this experience, is that being called 'weird', however unlikely, is unpleasant but tolerable; they can handle it.

Many people suffering from paranoid ideation have cognitive biases that interfere with a healthy perception of social situations. The cognitive bias 'jumping to conclusions', for instance, blocks the corrective experience that making eye contact is harmless and common behavior between people. Therefore, patients who jump to conclusions are trained to think of several alternative (neutral or positive) explanations while in a VR social environment with the misinterpreted stimuli present (making eye contact). Another common example is the 'attention to threat' bias. All attention is focused on the one guy who frowns, who is therefore identified as a potential threat. Patients who have a selective attention to threat are trained to divide their attention more equally over all stimuli present in the VR social environment; positive, neutral, negative and task-related. Since the occurrence and type of biases present varies greatly, VR exercises are always personalized.

Outline of the thesis

This thesis focusses on VR for research and treatment of psychosis. Before VR can be used in the treatment of paranoid ideation, the VR environments must be ecologically validated. To test this validity, 170 people with different levels of psychosis liability, and with different levels of paranoia and anxiety in daily life were exposed to interactive virtual social environments. Paranoid ideation and anxiety in response to several stressors in the virtual social environments were measured. The test of ecological validity is described in chapter 2. VR could help to better explore mechanisms and interaction effects in paranoid ideation. As mentioned, paranoid ideation needs to be studied in a social context. Factors such as cognitive biases do not exist in a vacuum, but are problematic because they negatively interact with the perception of social situations. If you see someone looking at you, this only becomes problematic if you jump to the conclusion that they know who you are and want to hurt you. The moderation of cognitive biases between social stress and paranoid ideation is investigated in chapter 3.

A common side effect of VR is the experience of cybersickness (CS): the occurrence of motion sickness-like symptoms when using VR. The occurrence of cybersickness is related to treatment dropout in VR therapy. The possible overlap between symptoms of CS and anxiety complicates findings. Research done on cybersickness sometimes seems contradictive and raises several questions. Chapter 4 investigates whether: (a) gender differences in CS can be replicated, (b) differences in anxiety and CS symptoms between patients and controls can be replicated, and (c) whether the relationship between exposure to VR and CS symptoms is mediated by anxiety.

The development of Virtual Reality-based Cognitive Behavioral Therapy (VR-CBT) and trial protocol can be found in chapter 5. We conducted a large multicenter randomized controlled trial to study VR-CBT treatment compared to standard treatment. A 116 patients with psychotic disorder suffering from paranoid ideation volunteered to participate in the study. Psychologists in seven Dutch mental health centers were trained in the VR-CBT protocol and provided with supervision. Since we wanted to measure the generalization of treatment effects on the daily life of the participants, ESM was used as primary outcome measure. The treatment effects of VR-CBT can be found in chapter 6. The cost-effectiveness and cost-utility analyses are presented in chapter 7.

Finally, in a general discussion chapter, we will summarize results, compare them to current literature and developments, reflect on strengths and limitations, and explore possible implications for the future.

2

Chapter 2

Environmental social stress, paranoia and psychosis liability: A virtual reality study

Wim Veling · Roos Pot-Kolder · Jacqueline Counotte · Jim van Os · Mark van der Gaag

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Abstract

The impact of social environments on mental states is difficult to assess, limiting the understanding of which aspects of the social environment contribute to the onset of psychotic symptoms and how individual characteristics moderate this outcome. This study aimed to test sensitivity to environmental social stress as a mechanism of psychosis using Virtual Reality (VR) experiments. Fifty-five patients with recent onset psychotic disorder, 20 patients at ultra-high risk for psychosis, 42 siblings of patients with psychosis, and 53 controls walked 5 times in a virtual bar with different levels of environmental social stress. Virtual social stressors were population density, ethnic density and hostility. Paranoia about virtual humans and subjective distress in response to virtual social stress exposures were measured with State Social Paranoia Scale (SSPS) and self-rated momentary subjective distress (SUD), respectively. Pre-existing (subclinical) symptoms were assessed with the Community Assessment of Psychic Experiences (CAPE), Green Paranoid Thoughts Scale (GPTS) and the Social Interaction Anxiety Scale (SIAS). Paranoia and subjective distress increased with degree of social stress in the environment. Psychosis liability and pre-existing symptoms, in particular negative affect, positively impacted the level of paranoia and distress in response to social stress. These results provide experimental evidence that heightened sensitivity to environmental social stress may play an important role in the onset and course of psychosis.

Introduction

The social environment influences the risk of onset, as well as the course of psychotic disorders[42]. Urban birth, childhood social adversity, neighborhood ethnic density, and social disorganization are risk factors for onset of psychosis[27,43-45]. Social stress may mediate these associations, given that psychosocial stress is associated with both risk of onset and relapse of psychosis[46,47]. Current theories of psychosis suggest that psychosis liability impacts individual sensitivity to experiences of social stress[48], in particular when the level of perceptual stimuli in the environment is high[49] and when the stress involves negative judgment of others[50]. Pre-existing (subclinical) paranoia, social anxiety, and negative affect may fuel this sensitivity, culminating in increasingly strong, sensitized psychotic responses to social stress exposure[48,51].

Experimental studies of patients with persecutory delusions found that paranoia increased when they entered a busy shopping street and that this effect was partly mediated by anxiety and depression[29,52]. Experience sampling studies showed associations between the occurrence of minor stressors in daily life and intensity of psychotic experiences in patients and, to a lesser extent, their first-degree relatives and the general population[51,53,54]. However, these approaches are not sufficient to investigate which aspects of the social environment contribute to the onset of psychotic symptoms and which individual characteristics moderate this outcome, as daily social environments are complex, never exactly the same, strongly influenced by the individual's behavior or presence of an observer, and cannot be controlled. Arguably the only way to test the mechanism of sensitized psychotic responses to the social environment, and the moderators thereof, would be to randomize individuals to controlled experimental environments with varying degree of social stress, quantifying environmental effect sizes as a function of liability to psychosis and prior level of (minor) symptoms. Virtual Reality (VR) technology, i.e., substituting sense data from the natural world with sense data about a virtual world that change in response to the user's actions, resulting in a "sense of presence" in an interactive 3-dimensional virtual world, offers the possibility to do so[1,52]. VR is relatively new in psychosis research, but several studies have shown that VR is feasible, safe and valid for psychotic disorders[55,56]. Recent studies found that paranoid response to a neutral virtual environment was higher in people at ultra-high risk for psychosis (UHR) than in healthy controls, and that paranoid ideations were associated with social defeat[57] and a history of bullying victimization[58].

In this study, we aimed to test social stress sensitivity as a mechanism of psychosis, by exposing individuals with different levels of liability to psychosis to 5 social stress environments in VR. We hypothesized that:

- Paranoia and subjective distress increase with degree of environmental social stress;

- Liability to psychosis, and (subclinical) psychotic and affective symptoms are associated with more paranoia and subjective distress in social environments; and
- Degree of environmental social stress interacts with psychosis liability and pre-existing symptoms on paranoia and subjective distress.

Methods

Participants

Individuals aged 18–35 years with different levels of liability to psychosis were included. We defined a high-liability group based on phenotype, i.e., the experience of (subclinical) psychotic symptoms. This group had 2 categories: (1) Patients with psychotic disorder, whose first diagnosis of psychotic disorder was established within the last 5 years. DSM-IV diagnosis was established with a semi-structured interview (SCAN; Schedules for Clinical Assessment in Neuropsychiatry[59] or CASH; Comprehensive Assessment of Symptoms and History[60]). All psychotic disorders were included, except for substance-induced psychotic disorder and psychotic disorder due to a medical condition; and (2) Patients at UHR for psychosis, according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) criteria[61]. The low psychosis liability group consisted of: (3) Siblings of patients with a psychotic disorder, who never had a psychotic episode themselves; and (4) Controls with a negative (first-degree family) history of any psychotic disorder. Exclusion criteria were a history of epilepsy, IQ lower than 75 and poor command of the Dutch language. Psychosis, UHR and sibling groups were recruited from 5 psychiatric institutes in the Netherlands. Controls were recruited with flyers at schools for vocational or higher education and in dentist offices in The Hague, and among the staff of a psychiatric institute in The Hague. Written informed consent was obtained from all participants. The study was approved by the medical ethical committee of Leiden University Medical Center.

VR set-up

The virtual environment was a bar with an indoor and an outdoor part (figure 2.1), built by CleVR with Vizard software[62]. Participants were standing during experiments and could turn around 360degrees. In order to walk around in the virtual environment, they used a Logitech F310 Gamepad. They wore a Sony HMZ-T1 Head Mounted Display with a HD resolution of 1280×720 per eye, with 51.6 diagonal field of view, a 3DOF tracker for head rotation, and built in headphones. Virtual humans (avatars) were sitting or standing at a table, chatted and had drinks. Bar background noises were played during the experiments.

Figure 2.1. Screenshot of the virtual bar environment. Source: CleVR.

Virtual social stressors

We created 3 sources of social stress in the virtual environment.

Population density: the number of avatars in the bar was variable, by which we could simulate population density and could manipulate level of perceptual stimuli. In the quiet, low stress condition, the number of avatars in the bar was 6. In the stressful, crowded situation, the number was 40.

Ethnic density: ethnic appearance of an avatar was Dutch or North African. In the low ethnic density condition, more than 80% of the avatars was Dutch for non-Dutch participants and North African for Dutch participants. In the high ethnic density condition, the ethnic distribution was the opposite.

Hostility: in the low-stress condition, avatars had a neutral facial expression. When participants approached, avatars looked only briefly at them, after which they resumed their activities. In the stressful condition, avatars looked in an angry, hostile fashion at participants for 5 seconds, as participants approached, and also at other, random, moments.

Experiments

All participants underwent 5 experiments of 4 minutes each, in a single session. In all experiments, they were instructed to explore the bar. Five avatars had a number (0–99) on their clothing. In order to engage participants in the experiment and to make them look at all avatars, they had to find these avatars, and to report the highest number and gender of the avatar with the highest number.

Virtual social stress was introduced at 4 levels:

- No stress—quiet, high ethnic density and neutral avatars;
- One stressor—crowded;
- Two stressors—(1) crowded and low ethnic density, (2) crowded and hostile avatars;
- Three stressors—crowded, low ethnic density and hostile avatars.

High population density was part of all stress conditions, because ethnic density and hostility could only be simulated effectively with a high number of avatars. The order of the experiments was random, except that the fifth experiment always had at least 2 stressors.

Measures

Baseline

Sociodemographic characteristics included age and sex. Ethnicity was defined as Dutch if the subject and both parents were born in the Netherlands, and as non-Dutch in all other cases. Level of education was classified as no/ primary education, vocational education ((V)MBO), higher secondary education (HAVO/VWO), higher tertiary education (HBO/University). Paranoia was assessed with the Green Paranoid Thoughts Scale (GPTS)[63], social anxiety with the Social Interaction Anxiety Scale (SIAS)[64] and minor positive, negative and depressive symptoms with the Community Assessment of Psychic Experiences (CAPE)[65].

During and after experiments

In order to assess how actively participants explored the virtual bar during the experiments, their position in the bar was recorded every second, and the distance between current and all other recorded positions was calculated. The average of these distance scores is an indication of distance covered during the experiments; the SD reflects the degree to which participants were at different positions in the bar.

After each experiment, participants were asked to rate their maximum momentary subjective distress during the experiment (SUD) in units on an analogue scale, with range 0 (no distress at all) to 100 (worst possible distress). Paranoid thoughts about avatars were measured after each experiment with the State Social Paranoia Scale (SSPS)[66].

Statistical analyses

All analyses were conducted with Stata version 11. Differences in sociodemographic characteristics and exploration behavior in the virtual bar between psychosis liability groups were tested with Chi square tests (categorical variables) and ANOVA (continuous

variables). For the analyses of the effects of virtual social stressors on paranoia and subjective distress, multilevel random intercept regression models were used, taking into account the repeated measure structure of the data. The B is the fixed regression coefficient of the predictor in the multilevel model. We analyzed the data using the multilevel random intercept XTREG procedure in Stata. First, effects of social stressors were investigated. For each subject, SSPS and SUD scores of experiments 3a and 3b (see Experiments) were summed together and divided by 2, in order to create average paranoia and distress scores for experiments with 2 stressors. Regression models were fitted with paranoia and peak subjective distress during experiments as dependent variables, number of stressors as independent variable and age, sex, level of education and psychosis liability as covariates. To estimate effect sizes of the separate stressors, Stata LINCOM procedure was used. Thus, the effect of population density was calculated by comparing stress level 2 with level 1, the ethnic density effect by comparing level 3a with level 2, and the effect of hostility by comparing level 3b with level 2. Second, differences in paranoia and subjective distress in VR between psychosis liability groups were examined. Third, associations between baseline symptoms and paranoia and distress in VR were explored, irrespective of psychosis liability group. Symptom domains were analyzed separately, but also entered simultaneously in a regression model, to test which baseline symptoms contributed most to paranoia and distress in VR. Fourth, interaction terms between social stress on the one hand, and psychosis liability and baseline symptoms on the other were added to the models. B coefficients of the main effects and the interaction terms were compared using the MARGINS dydx procedure, estimating linear marginal effects at the different virtual social stress levels.

Results

Fifty-three healthy controls, 42 siblings, 20 patients at UHR for psychosis, and 55 patients with psychotic disorder were included. Sociodemographic characteristics, baseline level of symptoms and use of psychotropic medication are shown in table 2.1. The UHR and psychosis groups had significantly higher levels of all symptoms than controls, and psychosis patients had a lower level of education. The proportion of males was much higher in the psychosis group than in the other groups.

ANOVA showed a difference between the psychosis liability groups in distance covered by participants during the experiments ($F = 2.864$, $df = 3$, $P = .039$). No statistically significant differences remained in post hoc Bonferroni corrected group comparisons (supplementary table S2.1). There was only a trend level significance of lower distance covered by the psychosis group compared to controls (mean difference 0.28, 95% CI, -0.01–0.57, $P = .063$). SD scores, indicating variation in positions, did not differ between groups.

Table 2.1. Characteristics of study sample

	Controls (N = 53)	Siblings (N = 42)	UHR (N = 20)	Psychosis (N = 55)
Sociodemographic				
Age	24.6 (4.4)	26.4 (4.8)	24.0 (4.5)	26.0 (4.7)
Male sex, n (%)	25 (47.2)	23 (54.8)	7 (35.0)	42 (76.4)[a]
Non-Dutch origin, n (%)	16 (30.2)	11 (26.2)	5 (25.0)	26 (47.3)
Level of education, n (%)				
No/primary	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.5)[a]
Vocational ((V)MBO)	13 (24.5)	11 (26.2)	8 (40.0)	25 (45.5)[a]
Higher secondary (HAVO/VWO)	10 (18.9)	4 (9.5)	5 (25.0)	10 (18.2)[a]
Higher tertiary (HBO/University)	30 (56.6)	26 (61.9)	7 (35.0)	17 (30.9)[a]
Symptoms[b]				
Paranoid thoughts	37.5 (9.1)	36.1 (6.1)	69.0 (26.6)[a]	56.2 (30.6)[a]
Social anxiety	16.8 (11.6)	15.6 (10.4)	38.6 (19.7)[a]	28.3 (16.1)[a]
Depressive symptoms	12.5 (2.8)	12.3 (2.2)	20.4 (4.7)[a]	14.8 (3.4)[a]
Positive symptoms	24.3 (4.6)	23.6 (3.1)	31.7 (7.5)[a]	31.2 (8.8)[a]
Negative symptoms	21.5 (4.6)	21.2 (3.7)	32.4 (7.9)[a]	27.1 (6.3)[a]
Use of psychotropic medication, n (%)[c]				
None	49 (94.2)	39 (92.9)	6 (30.0)	18 (32.7)
Antipsychotic	0 (0.0)	0 (0.0)	0 (0.0)	35 (63.6)
Antidepressant	1 (1.9)	1 (2.4)	12 (60.0)	5 (9.1)
Benzodiazepine	0 (0.0)	0 (0.0)	4 (20.0)	6 (10.9)
Other	2 (3.8)	2 (4.8)	5 (25.0)	2 (3.6)

Note. UHR, Ultra High Risk.
[a] P < .05, ANOVA or Chi-square test with post hoc comparisons, controls as comparison group.
[b] Paranoid thoughts assessed with Green Paranoid Thoughts Scale, Social Anxiety with Social Interaction Anxiety Scale, other symptoms with Community Assessment of Psychic Experiences.
[c] Self-report.

Virtual social stress elicited paranoid thoughts and subjective distress in participants. Table 2.2 shows that both measures increased with increasing numbers of virtual stressors. The B of the linear effect of number of social stressors on paranoia, adjusted for age, sex, level of education and psychosis liability, was 2.74 (95% CI, 2.31–3.17, P < .0005). The adjusted B of the linear effect of social stressors on subjective distress was 2.26 (95% CI, 1.52–3.00, P < .0005). Of the specific virtual stressors, population density (linear combination of experiment 2 compared to 1) had a strong positive effect on both paranoia and distress (table 2.3). Hostility (linear combination of experiment 3b compared to 2) was significantly and positively associated with paranoia, but not with subjective distress. Ethnic density (linear combination of experiment 3a compared to 2) was associated with neither paranoia nor distress.

Compared to subjects with low psychosis liability, those with high liability reported more paranoia and subjective distress in VR (table 2.3), B 3.62 (95% CI, 1.39–5.84) and 17.94 (10.99–24.90), respectively. Of the separate liability groups, only UHR

patients had significantly higher paranoia than healthy controls; the UHR and psychosis groups had higher levels of distress (figure 2.2).

Table 2.2. Paranoid thoughts and subjective distress in virtual reality, by degree and type of virtual social stress

Virtual social stress condition	Mean (SD)	B [a]	95% CI	P-value
Paranoia				
Number of stressors				
No stress	13.60 (6.2)	—	—	—
1 stressor	16.25 (8.1)	2.66	1.35–3.96	< .0005
2 stressors	16.78 (9.3)	3.17	1.85–4.49	< .0005
3 stressors	22.51 (11.4)	9.14	7.82–10.45	< .0005
Population density	—	2.65	1.31–3.99	< .0005
Ethnic density	—	0.55	-0.81–1.91	.426
Hostility	—	6.01	4.66–7.36	< .0005
Subjective distress				
Number of stressors				
No stress	26.96 (24.4)	—	—	—
1 stressor	32.81 (26.3)	5.41	3.11–7.71	< .0005
2 stressors	31.68 (25.0)	5.13	2.84–7.42	< .0005
3 stressors	34.48 (27.6)	7.60	5.30–9.90	< .0005
Population density	—	5.38	3.01–7.74	< .0005
Ethnic density	—	-1.35	-3.75–1.04	.269
Hostility	—	0.50	-1.87–2.89	.678

Note. [a] Multilevel random regression analysis regression coefficient B, adjusted for age, sex, ethnicity, level of education and psychosis liability; compared to the no stress condition. B coefficients of separate stressors calculated by comparisons of the linear effects of 2 conditions (see text).

Table 2.3. Paranoia and subjective distress in virtual reality, by psychosis liability group

	Paranoia			Subjective distress		
Psychosis liability group	B [a]	95% CI	P-value	B [a]	95% CI	P-value
Low[b]	—	—	—	—	—	—
High	3.62	1.39–5.84	.001	17.94	10.99–24.90	< .0005
Controls	—	—	—	—	—	—
Siblings	-1.86	-4.72–1.00	.203	–4.09	-13.02–4.83	.369
UHR	3.80	0.24–7.37	.037	17.90	6.68–29.13	.002
Psychosis	2.36	-0.43–5.16	.097	15.37	6.60–24.14	.001

Note. [a] Multilevel random regression analysis regression coefficient B, adjusted for age, sex, ethnicity, level of education and virtual experiment. Low liability and controls as reference groups.
[b] Healthy controls and siblings classified as low psychosis liability, UHR and psychosis as high liability.

Baseline levels of paranoid thoughts, social anxiety, (minor) positive, negative and depressive symptoms were all strongly associated with both paranoia and subjective distress in VR, with B's ranging from 0.13 to 2.68. When all baseline symptom domains

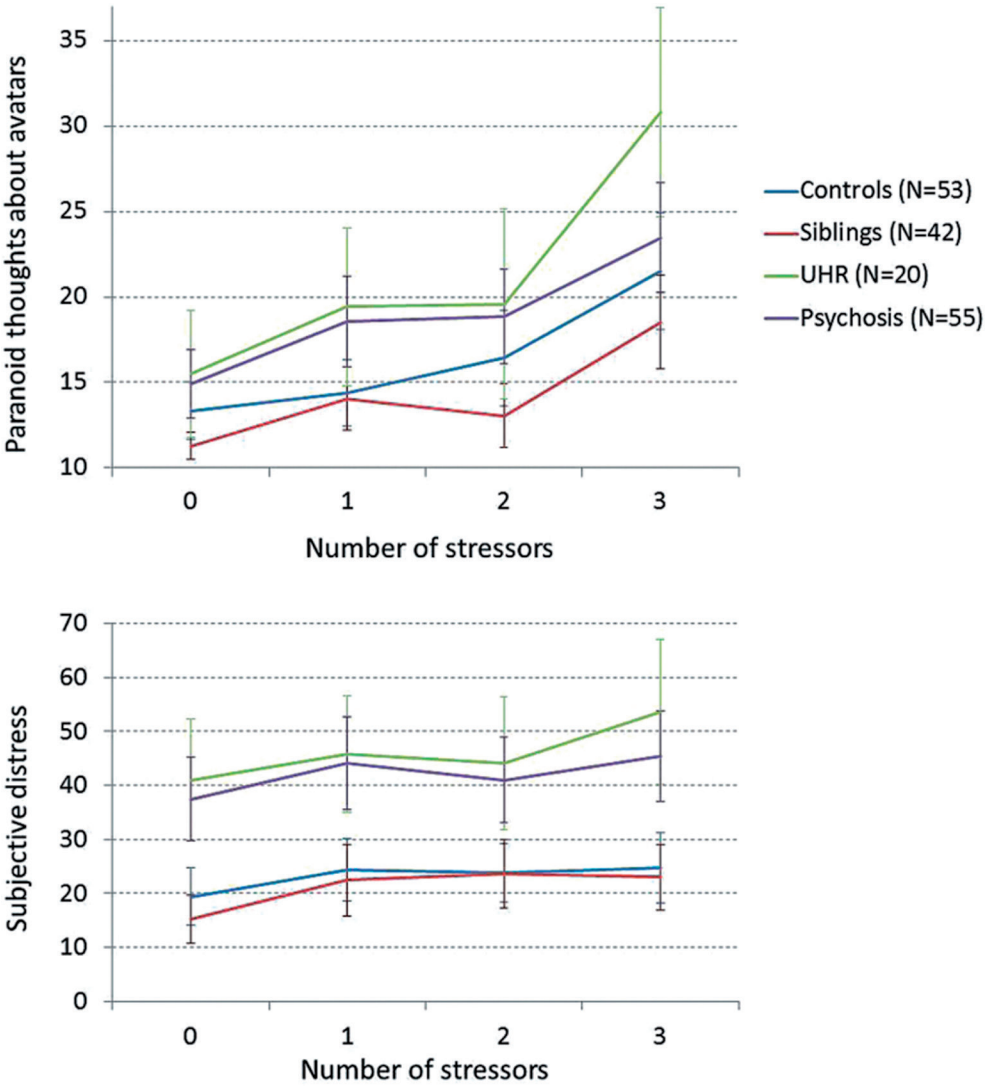

Figure 2.2. Paranoia and subjective distress in Virtual Reality (VR), by degree of virtual social stress and psychosis liability.

were entered simultaneously in the regression model, adjusted for age, sex, ethnicity, level of education and virtual experiment, paranoia in VR was predicted significantly only by depressive symptoms (B 0.60, 95% CI, 0.18–1.02, P = .005); subjective distress was associated only with social anxiety (B 0.39, 95% CI, 0.11–0.68, P = .007).

The effects of baseline symptoms on paranoia and subjective distress increased with level of virtual social stress. Adjusted interaction terms between social stress on the one hand and paranoid thoughts, social anxiety, positive, depressive and negative symptoms on the other, were all statistically significant, except for the interaction between social stress and

paranoid thoughts on subjective distress (P = .057). Table 2.4 shows how B coefficients of the linear marginal effects of symptoms increased at the different levels of social stress exposure. Strongest interaction effects were found with depressive symptoms. There was no significant interaction between social stress exposure and psychosis liability group, except for a stronger increase in paranoia with increasing social stress for the UHR group compared to controls (B interaction term 1.59, 95% CI 0.15–3.02, P = .03; B's of marginal effects UHR group compared to controls 1.56 [-2.57–5.69], 3.14 [-0.49–6.77], 4.73 [1.07–8.39] and 6.32 [2.10–10.53] for 0–3 social stressors, respectively).

Table 2.4. Effects of baseline symptoms on paranoid and stress response, at different levels of virtual social stress exposure

	Paranoid thoughts		Social anxiety		Depressive symptoms		Positive symptoms		Negative symptoms	
	B [a]	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Paranoia										
No stress	0.08	0.03–0.13	0.09	0.01–0.17	0.47	0.17–0.78	0.29	0.12–0.46	0.20	0.01–0.38
1 stressor	0.11	0.07–0.16	0.13	0.06–0.20	0.70	0.43–0.97	0.38	0.23–0.53	0.30	0.13–0.46
2 stressors	0.15	0.10–0.19	0.18	0.10–0.25	0.93	0.66–1.20	0.47	0.32–0.62	0.39	0.23–0.56
3 stressors	0.18	0.13–0.24	0.22	0.14–0.30	1.16	0.85–1.47	0.56	0.38–0.73	0.49	0.31–0.68
Subjective distress										
No stress	0.42	0.27–0.57	0.62	0.39–0.85	2.13	1.22–3.03	1.19	0.69–1.68	1.17	0.64–1.71
1 stressor	0.45	0.30–0.59	0.68	0.46–0.89	2.49	1.62–3.36	1.34	0.86–1.82	1.30	0.79–1.81
2 stressors	0.48	0.33–0.62	0.73	0.51–0.95	2.86	1.99–3.73	1.49	1.02–1.97	1.42	0.91–1.93
3 stressors	0.51	0.35–0.66	0.79	0.56–1.02	3.22	2.32–4.13	1.65	1.15–2.15	1.54	1.01–2.08

Note. [a] Multilevel random regression analysis, B coefficients, adjusted for age, sex, ethnicity and level of education, estimated using Stata margins dydx procedure, at the 4 levels of virtual social stress. All coefficients statistically significant (P < .05).

Discussion

This VR study provides experimental evidence of social stress sensitivity as a mechanism linking environment and psychosis. Paranoia and subjective distress increased with degree of social stress in the environment. High psychosis liability, pre-existing (minor) affective and, to a lesser degree, psychotic symptoms were associated with more paranoia and distress in social environments. Pre-existing symptoms had stronger impact on paranoia and distress when level of environmental social stress increased.

Strengths and limitations

The main strength of this study is the experimental design, using VR as a tool to study interactions between the individual and complex social environments. Environmental studies of psychosis are generally complicated by subjective retrospective information

about social environment and events. Momentary assessment studies are closer to the action, but cannot control occurrence of events and remain dependent on subjective information about the environment. This study was the first to expose individuals experimentally to controlled complex social environments with different degrees of social stressors. Environmental social stress exposures were identical for all participants, except for the ethnic appearance of avatars, which depended on the ethnicity of the participant. Type and degree of environmental stress were controlled. It should be noted that participants could avoid exposure to a certain degree, as they navigated through the environments themselves and were free to choose where to look. To minimize variation in exposure, participants had a simple task that required extensive exploration of the VR environment and the avatars. Recording data of the position of participants in the virtual bar during experiments suggest that distance and area covered did not differ substantially between psychosis liability groups.

The study had several limitations. The virtual environment was simulated, not photo-realistic and evidently still less complex than real life, which may reduce ecological validity. Previous studies, however, using similar VR software and environments, showed that experiences in these environments were correlated to real life experiences and symptoms, that participants reported all kinds of thoughts and feelings about avatars, and that virtual environments are sufficiently realistic to practice social behavior[56,67,68].

As there was no experiment without social stressors (e.g., noise), it cannot be ruled out that the amount of stimuli in VR was more important than the social nature of the stressors. The additional effect of avatars' hostile looks compared to a similar environment with neutral avatars, however, suggests that the social aspect of stressors does matter.

While the psychosis group had significantly higher paranoid thoughts and other symptoms than controls and siblings, their level of symptoms was lower than that of the UHR group, suggesting that many had already partially recovered. The majority of the psychosis group and nobody in the UHR group reported using antipsychotic medication, which may have contributed to the higher symptom level in the UHR group, and may have led to underestimation of the psychosis liability effect on paranoia and distress in VR. Another limitation is that the number of participants in the separate groups was relatively small, in particular in the UHR group, implicating that the analyses of separate group should be interpreted with caution.

Environmental social stress and psychosis

Current theories of psychosis state that environmental social stress contributes to the onset of psychosis by a process of sensitization, in interaction with liability to psychosis and subclinical symptoms[42,48,69]. This liability can be caused by genetic factors, or by perinatal or childhood environmental insults. Subsequent experiences of social stress may lead to an increasingly dysregulated dopamine system, as a result of which aberrant

salience is assigned to environmental stimuli. Negative affect, dysfunctional cognitive schemas and more stress will build up[70]. This vicious circle of sensitization and dopamine dysregulation eventually may lead to a psychotic state of delusions, hallucinations and negative symptoms[48]. Our study supports these theories in several ways.

First, environmental social stress elicited paranoia and subjective distress in a dose-response fashion. More VR stressors resulted in greater levels of paranoia and distress. Not all separate stressors, however, had the same impact. Population density and hostility were significantly associated with paranoia, and only population density with subjective distress. Ethnic density was related to neither outcome measure, possibly because the majority of the participants was Dutch (66%) and ethnic density effects have primarily been described among ethnic minorities[71]. In addition, our non-Dutch avatars had a North African appearance, whereas most non-Dutch participants had an ethnic background other than North African.

Second, paranoia and distress in VR were stronger in those with higher psychometric psychosis liability, phenotypically defined as having (subclinical) psychotic symptoms. Genetic risk for psychosis was not associated with paranoia and stress, as siblings had similar responses as controls. UHR patients had the strongest response to social stress exposure. Use of antipsychotic medication might explain the dampening of psychotic symptoms and distress in the FEP patients compared to the UHR group.

Third, minor negative, psychotic and in particular depressive symptoms predicted paranoia and distress in VR. Negative affective state was an important driver of the psychotic and stress response to social stress exposure. This is consistent with cognitive models of paranoia[70] in which negative affect is a core component in the development of paranoid delusions. An "affective route" to psychosis has been proposed, in which daily social stressors negatively influence affect, and disturbed affect in turn worsens biased appraisal of events and dysfunctional externalizing cognitions, eventually leading to paranoid delusions and other psychotic experiences[51]. Experience sampling studies also show that momentary negative affect predicts momentary paranoia in daily life[51].

Clinical implications

We have demonstrated that it is possible to expose patients with psychosis and UHR patients to complex virtual social environments, and that exposure to these environments leads to meaningful responses, which are associated with clinical symptom profile. Exposure therapy for paranoia can be envisioned, with gradual, controlled exposure to increasingly stressful and paranoia-inducing social situations simulated in VR. Our group is currently developing and testing such a VR exposure treatment. Several other pilot VR treatment studies have recently been published[55], it can be expected that more applications will be developed over the next few years.

The results of this study suggest that reactivity to daily social stress may be an important target for treatment in patients with high levels of psychosis liability. Reactivity may be modified by focusing on negative affect, biased appraisals and dysfunctional cognitive schemas in cognitive behavioral therapy, or by stress reduction techniques such as relaxation or meditation[72,73]. Preliminary VR stress management studies were published recently, suggesting that this may represent a promising approach for reducing stress reactivity[74,75].

Supplementary material

Supplementary table S2.1. Distance and area covered during the virtual experiments, by psychosis liability group

		N [a]	Mean	SD	F-score (df = 3)	P-value
Average distance	Controls	36	7.03	0.37		
	Siblings	33	6.96	0.41		
	UHR	15	7.04	0.34	2.864	0.039
	Psychosis	44	6.75	0.62		
Standard deviation of distance score	Controls	36	4.63	0.24		
	Siblings	33	4.59	0.30		
	UHR	15	4.64	0.15	1.168	0.325
	Psychosis	44	4.52	0.37		

[a] Only participants included who completed all experiments.

3

Chapter 3

Self-reported cognitive biases moderate the associations between social stress and paranoid ideation in a virtual reality experimental study

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Abstract

Introduction: Cognitive biases are associated with psychosis liability and paranoid ideation. This study investigated the moderating relationship between pre-existing self-reported cognitive biases and the occurrence of paranoid ideation in response to different levels of social stress in a virtual reality environment.

Methods: This study included 170 participants with different levels of psychosis liability (55 recent onset psychosis, 20 ultrahigh risk for psychosis, 42 siblings of psychotic patients, and 53 controls). All participants were exposed to virtual environments with different levels of social stress. The level of experienced paranoia in the virtual environments was measured with the State Social Paranoia Scale. Cognitive biases were assessed with a self-report continuous measure. Also, cumulative number of cognitive biases was calculated using dichotomous measures of the separate biases, based on general population norm scores.

Results: Higher belief inflexibility bias ($Z = 2.83$, $P < .001$), attention to threat bias ($Z = 3.40$, $P < .001$), external attribution bias ($Z = 2.60$, $P < .001$), and data-gathering bias ($Z = 2.07$, $P < .05$) were all positively associated with reported paranoid ideation in the social virtual environments. Level of paranoid response increased with number of cognitive biases present ($B = 1.73$, $P < .001$). The effect of environmental stressors on paranoid ideation was moderated by attention to threat bias ($Z = 2.78$, $P < .01$) and external attribution bias ($Z = 2.75$, $P < .01$), whereas data-gathering bias and belief inflexibility did not moderate the relationship.

Conclusion: There is an additive effect of separate cognitive biases on paranoid response to social stress. The effect of social environmental stressors on paranoid ideation is further enhanced by attention to threat bias and external attribution bias.

Introduction

There is a relationship between exposure to stressful social environments and risk for developing psychosis[42,76]. Associations with psychosis have been documented for childhood abuse[77], recent stressful life events[78], social defeat[57], belonging to an ethnic minority group[79,80], urban upbringing[81], and being a victim of bullying[58]. As a result of long-term or repeated exposure to stressful social environments, cognitive biases, such as an increased attention for potential threat, may develop. Psychological models suggest that cognitive biases increase vulnerability to develop paranoid ideations or delusions when confronted with environmental social stress later in life[48,82].

Psychotic disorders are characterized by both cognitive deficits[83,84] and cognitive biases[82]. Cognitive deficits are impairments in cognitive functioning, such as problems with verbal memory[83]. Cognitive biases represent selective processing of information, such as the tendency to attend to a certain type of stimulus or consistently interpret emotionally ambiguous information in a negative direction[85]. Cognitive biases are implicated in developing and maintaining paranoid ideation[14]. Paranoid ideation characterizes 90% of patients with psychotic disorder[18]. Psychotic patients with paranoid delusions anticipate intentional harm inflicted by other people. Cognitive models of paranoia propose that cognitive biases distort the processing of information from the social environment toward a more paranoid interpretation[48]. Several types of cognitive biases are associated with paranoid ideation[82]. Cognitive biases are measured with experimental tasks; only recently have self-report measures been developed and validated against experimental tasks[86-88]. "Data-gathering bias" (also known as "jumping to conclusions") is a cognitive bias characterized by hasty decision making. "Belief inflexibility" is a cognitive bias that results in rigidity of beliefs when exposed to contradictory evidence; it overlaps with confirmatory bias and the bias against disconfirmatory evidence[89]. The tendency to attend selectively to threat-related information is known as "attention to threat bias." "External attribution bias" is the tendency to blame other people for negative events. All of these four biases were found to be more prevalent in patients with a schizophrenia spectrum disorder[82,90-93] and in people with subclinical psychotic symptoms at ultrahigh risk for psychosis (UHR)[94-97] than in healthy controls. They seem specifically related to the development and maintenance of paranoid delusions[14]. These findings suggest that the level of cognitive biases is associated with the level of paranoid ideation in response to social stressors in the environment, in particular in patients with a psychotic disorder and UHR.

Some evidence for this psychopathological mechanism is derived from experimental and time-sampling studies. In an experimental study, when patients with persecutory delusions were exposed to a crowded street in inner London, they reported an increase in paranoid ideation, auditory hallucinations, and in data-gathering bias[52]. Time-sampling studies using observations in daily life found a temporal association between social contact and paranoid ideation[53]. However, due to the complexity of interactions

between personal and contextual factors, it is difficult to examine the context of paranoid ideation in daily life social environments. Ideally, the interaction between social environments, cognitive biases, and paranoid ideation should be explored using an experimental design, in which exposure to social stress is controlled.

Virtual reality (VR) allows systematic manipulation of social environments[98]. VR is a safe and valid method to investigate paranoia in healthy individuals, in UHR patients, and in patients with persecutory delusions[56,62]. Recent research has demonstrated that virtual social stressors were able to elicit paranoid ideation in VR social environments[62,99,100] and psychosis liability and pre-existing negative affect moderated the levels of paranoia and distress[100].

The present study manipulated the number of social stressors presented in the virtual environment. The moderating effect of cognitive biases on the association between the number of social stressors and paranoid ideation was examined in groups with a different liability to psychosis. Our hypothesis was that the level and number of cognitive biases present will be positively associated with the level of paranoid ideation when participants are exposed to increased social stress.

Methods

Participants

Four groups of participants (aged 18–35 years) with different liability to psychosis were recruited. Namely, a group with high liability for psychosis consisting of (1) patients with recent onset psychotic disorder (N = 55) and (2) patients with an UHR status (N = 20); as well as a group with low liability for psychosis with (3) siblings of patients with a psychotic disorder, who had never had a psychotic episode themselves (N = 42), and (4) healthy controls without a history of psychotic disorder or a first-degree relative with a psychotic disorder (N = 53). The exclusion criteria were poor command of the Dutch language, a history of epilepsy, and an IQ ≤ 75.

This study was approved by the Medical Ethics Committee of the Leiden University Medical Centre (NL37356.058.12/P12.182). Written informed consent was obtained from all participants.

The psychotic group included individuals with a recent (< 5 years) diagnosis of a psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), with the exception of substance-induced psychotic disorder and psychotic disorder due to a medical condition. They were recruited from five participating mental health services. The UHR group included individuals with an UHR status, who were recruited among patients seeking help for nonpsychotic psychiatric symptoms at

two mental health services. The siblings group included siblings of persons diagnosed with a psychotic disorder, who did not themselves have a personal history of psychotic disorder or meet UHR criteria. The healthy control group included persons recruited from the general population without a history of psychotic disorder or a first-degree relative with a psychotic disorder.

Measurement instruments

Diagnostic Instruments. The Comprehensive Assessment of At-Risk Mental States (CAARMS)[61] was used to assess UHR status. The CAARMS identifies three inclusion groups: (1) people with a schizotypal personality disorder and/or a first-degree relative with psychosis; (2) people that experience attenuated positive psychotic symptoms, such as paranoid ideas and unusual perceptual experiences; and (3) people who have experienced a brief psychotic episode lasting ≤ 1 week and remitted without treatment with antipsychotic medication. Additional inclusion criteria were either a recent drop of 30% in social functioning as assessed with the Social and Occupational Functional Assessment Scale (SOFAS)[101,102] or dropping below a score of 55 on the SOFAS.

Psychotic disorder was diagnosed with either the Comprehensive Assessment of Symptoms and History (CASH)[60] or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)[59]. CASH and SCAN are similar semi structured interviews for diagnosing psychotic disorders, following DSM and ICD diagnostic criteria. Choice of instrument varied per participating mental health center.

Cognitive biases

At baseline, the Davos Assessment of Cognitive Biases Scale (DACOBS) was administered to assess cognitive biases[87]. The DACOBS is a self-rating assessment scale, consisting of seven subscales (four cognitive biases, two assessing subjective deficits in cognition and social cognition, and one on safety behaviors). In this study, we used the four subscales that measure cognitive biases, i.e., (1) data-gathering bias, (2) belief inflexibility bias, (3) selective attention to threat bias, and (4) external attribution bias. The subscales had an acceptable reliability (Cronbach's alpha ranging from .64 to .72) and an acceptable convergent validity (Spearman's Rho ranging from .36 to .63). Factor analysis confirmed that the four cognitive biases are separate constructs[87]. All factors independently explained the variance (eigenvalues > 2) and total explained variance was 45%. The DACOBS was cross-validated with correlations ranging from .360 to .627. The beads task, a probabilistic inference task[103], was used as a validation test for the "Jumping to conclusions" subscale ($r = -.360$, $P < .01$). The Dogmatism scale, a self-report measurement, was used to validate the Belief inflexibility bias ($r = .403$, $P < .01$). The Green Paranoid Thoughts Scale, a self-report measurement, has two subscales. Subscale A measures ideas of social reference and subscale B measures paranoid thoughts. Part A

was used to validate the Attention to threat bias ($r = .408$, $P < .01$), whereas subscale B was used to validate the External attribution bias ($r = .627$, $P < .01$). The factor structure was replicated in an independent sample by confirmative factor analysis[88].

A cognitive bias was considered to be present in a participant when the score was "above average," "high," or "very high" according to the norm scores for the normal control population[87]. The number of elevated cognitive biases was summed to create a cumulative cognitive biases variable.

State paranoia

Immediately after exposure to each virtual social environment, momentary paranoia was assessed using the Social State Paranoia Scale (SSPS). The SSPS is a valid (Spearman's rho is .41) and reliable (Cronbach's alpha is .91) measure of state persecutory ideation in virtual social environments[66].

VR setting

The virtual environment used was a café with both indoor and outdoor areas. Participants could navigate in the virtual environment, using a Logitech F310 Gamepad. For VR display, participants used the Sony HMZ-T1 Head-Mounted Display with a HD resolution of 1280 × 720 (per eye), with 51.6 diagonal field of view, a 3DOF tracker for head rotation, and built-in headphones. The researcher controlled the VR system using a graphical user interface, whereby several actions could be activated within the virtual environment. Avatars could be placed in the café and chatted among themselves while sitting or standing at a table. Sounds and café noises were audio-played in the background. The avatars looked at participants for 5s when they were approached.

Experiments

The number of social stressors in the virtual social environments was manipulated by (1) the number of avatars in the virtual environment (6 or 40 avatars); (2) own ethnic or other ethnic identity of the avatars; and (3) neutral or hostile facial expressions by the avatars. Pre-existing cognitive biases were measured with a self-reported questionnaire before participants were exposed to the virtual environments with a varying number (0–3) of social stressors. Paranoid ideation was assessed after each exposure session of 4 min.

To engage participants in the virtual social environment, the computer randomly assigned a number (0–99) to five of the avatars. Participants were encouraged to explore the VR environment and to remember the number and sex of the avatar assigned the highest number. In a small pilot, patients reported that the task was easy and not stressful or distracting. All participants participated in four conditions with exposure to no, one, two, or three social stressors in the VR environment. The order of exposure to the different conditions was randomized.

Detailed information on the conditions have been published previously[100].

Statistical analyses

Analysis was performed using Stata version 13. Differences in age between the psychosis liability groups were tested with one-way ANOVA. Group differences in the dichotomous variables sex, ethnic minority status, and education were tested using χ^2 tests. Multilevel random intercept regression analysis was conducted to test associations between cognitive biases and paranoid ideations in VR using the XTREG procedure in Stata. The study data have a hierarchical structure, with repeated measurements (level 1) nested within individuals (level 2). Multilevel analyses take into account that observations within an individual are more similar than those between individuals. The interaction effects between the number of virtual stressors and cognitive biases were added to the multilevel regression models to investigate a moderating relationship with sex, age, level of education, and psychosis liability as covariates. We examined whether the interaction between level of cognitive bias and level of social stress significantly predicted paranoid ideation. If moderation analysis found a significant interaction for different levels of cognitive biases, post hoc probing analysis was conducted to see how the different levels of cognitive biases (high vs low) affected the association between social stress and paranoid ideation[104].

Results

Sociodemographic characteristics of the participants and level of cognitive biases are presented in table 3.1. Patients with psychosis had (on average) a lower level of education than siblings or the healthy controls. The proportion of males was high in the psychosis group (76%) and low in the UHR group (35%). Overall, males reported a higher level of data-gathering bias than females (M 25.5 vs F 22.9, P = .006). The covariate effect of sex was nonsignificant.

Participants with higher psychosis liability scored higher on attention to threat, belief inflexibility, and external attribution, while participants with lower psychosis liability scored average or below average. There was no psychosis liability effect on data-gathering bias, i.e., all groups scored average and showed no statistical differences; the results are shown in table 3.2.

The association between cognitive biases and paranoid ideation is shown in table 3.3. All four types of cognitive biases were significantly associated with higher levels of paranoid ideation experienced in the VR environments (table 3.3a).

Forty-four percent of the low-liability group had no cognitive biases, compared to only 9% in the high-liability group. A significant effect was found for cumulative number of

Table 3.1. Sociodemographic characteristics of the study sample

	Controls N = 53	Siblings N = 42	UHR N = 20	Psychosis N = 55		P
Sex male, n (%)	25 (47.2)	23 (54.8)	7 (35)	42 (76.4)	χ^2 (3) = 14.5	**.002**
Age in years	25 (4)	26 (5)	24 (4)	26 (5)	F (df) = 2.1 (3)	.097
Non-Dutch origin, n (%)	16 (30.2)	11 (26.2)	5 (25)	26 (47.3)	χ^2 (3) = 6.3	.099
Level of education, n (%)					χ^2 (9) = 19.7	**.020**
No/primary	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.5)		
Vocational ((V)MBO)	13 (24.5)	11 (26.2)	8 (40)	25 (45.5)		
Higher secondary (HAVO/VWO)	10 (18.9)	4 (9.5)	5 (25)	10 (18.2)		
Higher tertiary (HBO/University)	30 (56.6)	26 (61.9)	7 (35)	17 (30.9)		
Medication use[a], n (%)						
None	49 (94.2)	39 (92.9)	6 (30.0)	18 (32.7)		
Antipsychotic	0 (0.0)	0 (0.0)	0 (0.0)	35 (63.6)		
Antidepressant	1 (1.9)	1 (2.4)	12 (60.0)	5 (9.1)		
Benzodiazepine	0 (0.0)	0 (0.0)	4 (20.0)	6 (10.9)		
Other	2 (3.8)	2 (4.8)	5 (25.0)	2 (3.6)		

Note. Values are presented as mean (standard deviation; SD) or N (%). P-values are given from ANOVA (for continuous variables) and tested with Bonferroni correction, or χ^2 tests (for categorical variables). UHR, patients with ultra-high risk for psychosis. Bold values are significant at < .05.
[a] Self-report.

Table 3.2. Group differences in pre-existing self-reported cognitive biases measured with the DACOBS

	Controls N = 53	Siblings N = 42	UHR N = 20	Psychosis N = 55	F (df)	P
Data-gathering bias (SD)	24.2 (6.1)	23.9 (6.7)	24.6 (5.4)	24.8 (6.3)	0.2 (3)	.911
Belief inflexibility bias (SD)	14.2 (4.9)	13.3 (4.4)	18.1 (5.1)	19.7 (6.9)	14.2 (3)	**< .001**
Attention to threat bias (SD)	17.8 (7.5)	16.1 (5.7)	28.8 (6.9)	22.8 (7.4)	13.5 (3)	**< .001**
External attribution bias (SD)	14.1 (4.9)	12.3 (3.9)	23.2 (5.1)	19.8 (7.7)	25.3 (3)	**< .001**

Note. DACOBS, Davos assessment of cognitive biases scale. DACOBS values are presented as mean (standard deviation; SD). P-values are given from ANOVA. Biases were tested with Bonferroni correction. Bold values are significant at < .05.

cognitive biases on reported paranoid ideation (B = 1.73, 95% CI: 0.93–2.53, P < .001). Effect of cumulative number of biases is shown in table 3.3b.

We found a significant interaction effect between the number of cognitive biases and the number of social stressors on paranoid ideation B = 0.52, 95% CI: 0.22–0.82, P = .001).

We found a significant interaction effect between attention to threat bias and the number of social stressors on paranoid ideation (P < .01) and also a significant interaction effect between external attribution bias and the number of social stressors on paranoid ideation in the VR environment (P < .01). The interaction results are shown in table 3.4.

Table 3.3. Effect of pre-existing self-reported cognitive biases, on paranoid ideations reported in virtual social stress environments

Paranoia SSPS	Coefficient[a]	Standard error	Z	P	95% Confidence Interval	
Type of bias[a]						
Data-gathering bias	.183	.089	2.07	**.039**	.00948	.35649
Belief inflexibility bias	.288	.101	2.83	**.005**	.08888	.48726
Attention to threat bias	.262	.077	3.40	**.001**	.11113	.41379
External attribution bias	.253	.097	2.60	**.009**	.06247	.44400
Cumulative number of biases[b]						
One	.074	1.57	.05	.962	-3.0090	31.579
Two	3.056	1.56	1.96	**.050**	-.00493	61.162
Three	5.995	1.77	3.39	**.001**	25.256	94.636
Four	5.828	1.81	3.22	**.001**	22.843	93.714

Note. SSPS, Social State Paranoia Scale. Bold values are significant at < .05.

[a] B coefficient in multilevel random regression analysis (cognitive bias). Analyses were adjusted for sex, education, age, and psychosis liability.

[b] Calculated using dichotomous measures of the separate biases, based on general population norm scores, no cognitive biases as reference category.

Table 3.4. Interaction effect between cognitive biases and level of social stress, on paranoid ideations reported in virtual social stress environments

Paranoia SSPS	Coefficient[a]	Standard error	Z	P	95% Confidence Interval	
Data-gathering bias	.052	.036	1.45	.148	-.01842	.12231
Belief inflexibility bias	.038	.036	1.05	.292	-.03271	.10861
Attention to threat bias	.079	.028	2.78	**.005**	.02337	.13452
External attribution bias	.090	.033	2.75	**.006**	.02583	.15366

Note. Bold values are significant at < .05.

[a] B coefficient in multilevel random regression analysis (cognitive bias × number of social stressors). Analyses were adjusted for sex, education, age, and psychosis liability.

Post hoc probing showed that both low and high levels of attention to threat bias significantly affected the association between social stress and paranoid ideation (low: B = 2.21, 95% CI: 1.62–2.80, P < .001; high: B = 3.43, 95% CI: 2.81–4.05, P < .001). Post hoc probing shows that both low and high levels of external attribution bias significantly affect the association between social stress and paranoid ideation (low: B = 2.19, 95% CI: 1.59–2.79, P < .001; high: B = 3.43, 95% CI: 2.81–4.06, P < .001). The effect of the difference in slopes is presented in figure 3.1. A high level of attention to threat bias showed a stronger paranoid response to an increase in social stressors. A high level of external attribution bias also showed a steeper paranoid response to an increase in social stressors.

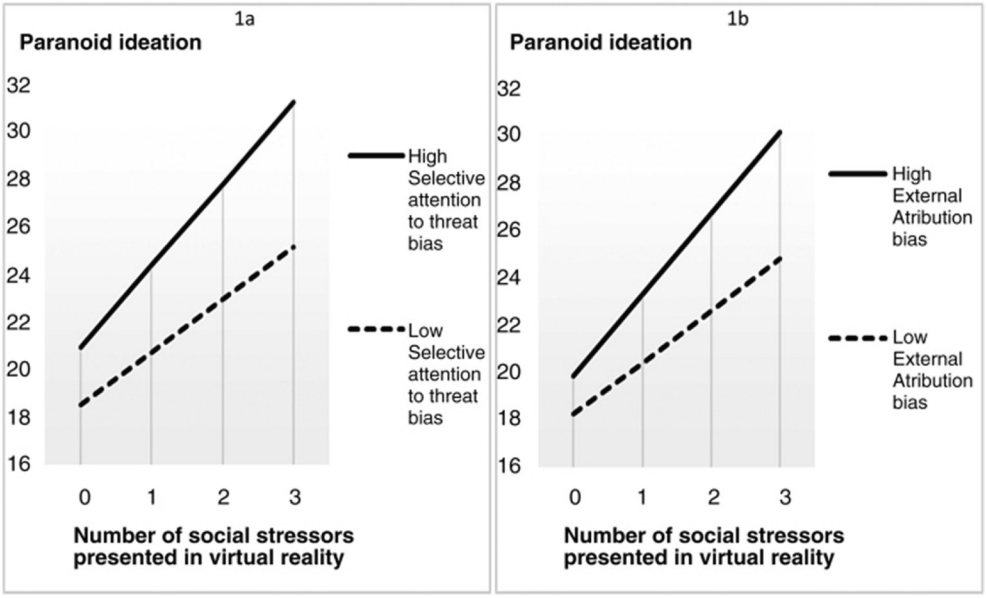


Figure 3.1. The moderating effect of high versus low self-reported cognitive biases on the association between number of social stressors presented in virtual reality (0–3) and elicited paranoid ideation (Social State Paranoia Scale).
Note. Analyses were adjusted for sex, education, age. and psychosis liability.

Discussion

In this experimental VR study, higher psychosis liability was associated with higher levels of the cognitive biases attention to threat, belief inflexibility, and external attribution but not with data-gathering bias. Also, belief inflexibility, attention to threat, external attribution bias, and data-gathering bias all predicted paranoid ideation in controlled virtual social environments. When more cognitive biases were present that person showed a stronger paranoid response. Both attention to threat and external attribution bias moderated the paranoid response during exposure to social environmental stress (figure 3.1).

By using VR to fully control the level of exposure to social stressors, this study found experimental evidence to support current cognitive psychological models[14,48] of the development and persistence of paranoid delusions. When people are exposed to social stress in the environment, higher levels of attention to threat bias and external attribution bias contribute to a more paranoid interpretation of the social environment. When multiple cognitive biases are present, this increases the paranoid interpretation.

In accordance with previous research, the present study found a positive relationship between the presence of cognitive biases and the experience of paranoid ideation. However, there was no significant difference in scores for data-gathering bias between

the four groups with different psychosis liability. This may indicate poor sensitivity of the DACOBS subscale to measure data-gathering bias. Although the DACOBS data-gathering bias subscale is validated against the beads task, their shared variance is limited[87]. Other explanations may be the fact that data-gathering bias may be difficult to measure using a self-report questionnaire, as those with the bias, compared with those without the bias, do not differ in the self-rated level of decisiveness[105]. Not finding different levels of data gathering in different liability groups is at odds with the literature, but finding a marginally significant effect of data gathering on paranoid ideation and no moderating effect is in accordance with the meta-analytical findings[106]. Our findings suggest that data-gathering biases may not be as relevant in the model of paranoid symptoms as was formerly expected.

Although we found a significant difference for belief inflexibility bias between the groups with different psychosis liability, there was no interaction effect between environmental social stress and belief inflexibility bias on paranoid ideation. Apparently, the relationships between specific cognitive biases and paranoid ideation differ. Cognitive biases describe selective processing of information in general; subdivision into more specific categories may improve our understanding of the cognitive processes involved in paranoid ideation.

Strengths and limitations

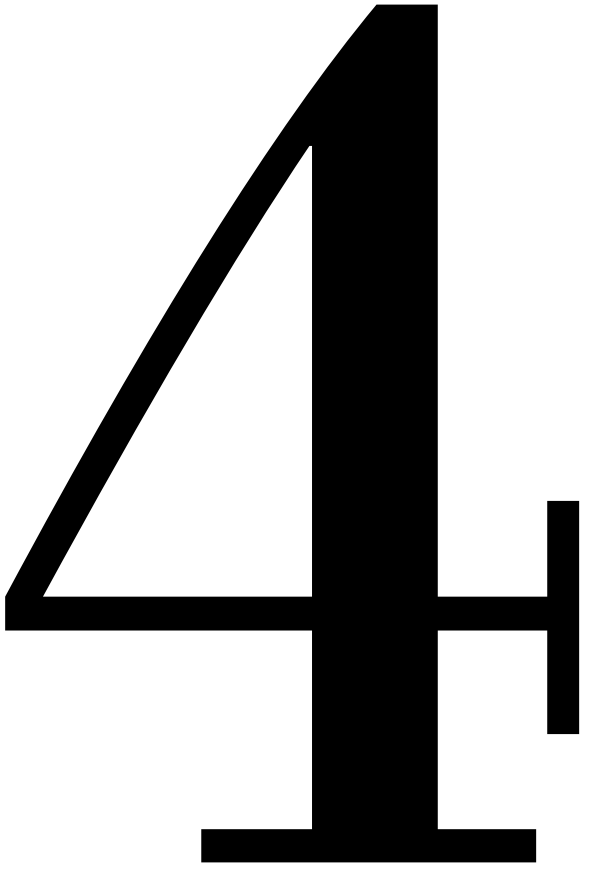
The main strength of this study is the use of VR to control the social environments and the social stressors the participants are exposed to. All participants were exposed to exactly the same environmental conditions, which would be impossible in a real-life social situation. The use of VR also prevents unintended effects of interactions between the participant and the social environment, allowing us to study the effect of cognitive biases on paranoid ideation. An additional strength is the variety of participants with different liability to psychosis, allowing to investigate the relationship between cognitive biases, social stress, and paranoid ideation over different levels of psychosis liability.

The study has several limitations. First, cognitive biases were assessed using self-report questionnaires only. Also, only 20 participants were included in the UHR group and this group consisted mainly of females. Our psychosis sample consisted of patients with recent onset psychosis only and was mainly males. The differences in sex distribution in these groups are consistent with previous research[102,105] and may have influenced the results in the high psychosis liability group. This study used the facial expressions of the avatars to convey hostility; however, since facial affect recognition impairments are found in patients with a first episode of psychosis[107], this may have affected the results in our high-liability group. Difficulty with interpreting the avatars' hostile faces may have caused additional anxiety or may have influenced the effect between social hostility and paranoid interpretation. Also, although the categories of cognitive biases were based on exploratory factor analysis[87] and replicated in confirmatory factor

analysis in another sample[88], it is important to note that these biases likely interact and possibly partially overlap. Moreover, this study is limited to four cognitive biases. For example, we did not include interpretation bias, which is the tendency to draw negative conclusions when presented with ambiguous information[108]. Interpretation bias occurs in a nonpsychiatric population with higher psychosis vulnerability and may be associated with paranoid ideations[109]. Prevalence and severity of cognitive biases were too small in the low-liability group to analyze high- and low-liability groups separately. The effects remained statistically significant when psychosis liability was included as a covariate in the regression models, suggesting that cognitive biases predict paranoid response to social stressors independent of psychosis liability. Further research is needed to investigate this issue. Last, we only included patient groups with UHR or a diagnosis of psychotic disorder, whereas paranoid ideations are also common in other psychiatric disorders. Inclusion of a broader range of psychiatric disorders may help to increase the understanding of paranoia.

Clinical implications

Both attention to threat bias and external attribution bias are viable targets for interventions in cognitive behavioral therapy, aiming to mitigate the effect of these biases on paranoid appraisal of the social environment. Patients could be trained to normalize their attention to threat bias. However, as findings on the effect of specific techniques are not consistent further development is needed[110-112]. External attribution can be explored and competing explanations may be generated and tested with behavioral experiments. Interestingly, these procedures implicitly address belief inflexibility by contrasting several different beliefs with an event. In patients suffering from paranoid ideation, belief inflexibility has indeed been found to improve with cognitive behavioral therapy[113]. Psychological therapy in a VR social environment would allow us to integrate exposure to social situations with an active correction of dysfunctional cognitions. Such cognitive behavioral therapy enhanced by VR (VR-CBT) is currently under investigation[114,115].



Chapter 4

Anxiety partially mediates cybersickness symptoms in immersive virtual reality environments

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Abstract

The use of virtual reality (VR) in psychological treatment is expected to increase. Cybersickness (CS) is a negative side effect of VR exposure and is associated with treatment dropout. This study aimed to investigate the following: (a) if gender differences in CS can be replicated, (b) if differences in anxiety and CS symptoms between patients and controls can be replicated, and (c) whether the relationship between exposure to VR and CS symptoms is mediated by anxiety. A sample (N = 170) of participants with different levels of psychosis liability was exposed to VR environments. CS and anxiety were assessed with self-report measures before and after the VR experiment. This study replicated gender differences in CS symptoms, most of which were present before exposure to VR. It also replicated findings that a significant correlation between anxiety and CS can be found in healthy individuals, but not in patients. In a VR environment, anxiety partially mediated CS symptoms, specifically nausea and disorientation. A partial explanation for the differences found between patients and controls may lie in a ceiling effect for the symptoms of CS. A second explanation may be the partial overlap between CS symptoms and physiological anxiety responses. CS symptoms reported at baseline cannot be explained by exposure to VR, but are related to anxiety. Caution is required when interpreting studies on both CS and anxiety, until the specificity in measurements has been improved. Since anxiety mediated the CS symptoms, CS is expected to decline during treatment together with the reduction of anxiety.

Introduction

The use of virtual reality (VR) in psychological treatment is expected to increase now that affordable technologies are available for clinical implementation[6]. VR can be more effective and less burdensome for patients[116] and more practical for therapists[117] than in vivo (real-life) exposure therapies. The use of VR in treating psychological disorders was introduced about 20 years ago[5]. This led to studies on VR treatment for various anxiety disorders[7], eating and weight disorders[118], depression[119], autism spectrum disorders[120], and substance-related disorders[121], as well as paranoid ideation[115] and hearing voices[122] in psychotic disorders. An important factor contributing to the effect of VR treatment is immersion, that is, the sense of being present in the virtual environment[123]. However, a common drawback of using head-mounted displays as a medium for immersive VR environments is the experience of cybersickness (CS)[2], also known as simulator sickness. CS is the occurrence of motion sickness-like symptoms when using VR and is related to increased treatment dropout[6]. As CS symptoms occur in 60 to 70 percent of participants[124], this has a negative impact on treatment effects. CS is an unintended negative side effect and efforts should be made to limit negative effects while preserving the therapeutic effect of VR[125]. Four factors are reported to influence the occurrence of CS: (1) hardware and software choices for the VR system, (2) design of the virtual environment, (3) task characteristics, and (4) user characteristics[125,126]. Examples of hardware and software characteristics influencing CS are visual surround of the display[127] and navigation (e.g., a mouse, joystick or treadmill)[128]. The design of the virtual environment can influence CS by using dynamic auditory stimulation[129] and allowed movement (active vs. passive)[125]. Task characteristics known to influence CS are duration of exposure to the virtual environment[130] and training[131]. User characteristics that can influence CS include gender, affective symptoms, and mental health. Susceptibility to CS is increased for women and varies over the menstrual cycle due to hormonal variation; however, explanations for this gender difference are incomplete[132]. Affective symptoms (e.g., feeling stressed or anxious) may increase the experience of CS[133,134] but the nature of this relationship remains unclear. VR treatment is used to expose patients to a virtual representation of their feared stimuli. During VR treatment patients will therefore experience high levels of anxiety. Physiological symptoms of anxiety and CS overlap and may confound both scientific research[134] and clinical practice. Anxiety disorders are much more prevalent in women[135], making gender-specific relationships between CS, anxiety, and VR used in psychological treatment, an area of interest. It is also unclear why different findings emerge in healthy individuals and patients. For example, significant correlations between levels of experienced anxiety and CS were found in healthy controls[136], but not in patients diagnosed with persecutory delusions exposed to a neutral VR environment[137]. High levels of CS symptoms were found in patients with an anxiety disorder even before immersion in VR[138]. Correlations were found between some CS symptoms and reported anxiety in a sample with both healthy controls and

patients with an anxiety disorder[139]. Some CS symptoms may reflect anxiety more than side effects[140]. Thus, more clarity is required as to which user characteristics influence CS. The present study aimed to investigate the following: (a) if gender differences in CS can be replicated, (b) if differences in anxiety and CS symptoms between patients and controls can be replicated, and (c) whether the relationship between exposure to VR and CS symptoms is mediated by anxiety (figure 4.1).

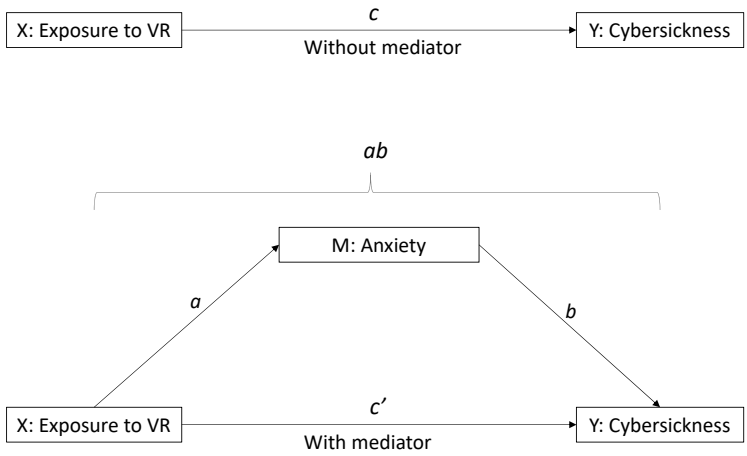

Figure 4.1. Mediation hypothesis.
Note. VR = virtual reality.

Materials and methods

Participants

A total of 170 participants aged 18–35 years were earlier recruited for a large VR study[100]. From these, we defined a high liability patient group based on phenotype, that is, the experience of (subclinical) psychotic symptoms. This group consisted of two categories:

- Fifty-five patients with a psychotic disorder according to the DSM-IV, with the exception of substance-induced psychotic disorder, and psychotic disorder due to a medical condition. These patients were recruited at five outpatient departments.
- Twenty patients with an at-risk mental state (ARMS), recruited among patients seeking help for nonpsychotic psychiatric problems at two outpatient departments.

The low psychosis liability control group consisted of:

- Forty-two siblings of people diagnosed with a psychotic disorder who had no personal history of a psychotic disorder themselves.

- Fifty-three control persons recruited from the general population; they had no history of psychotic disorder nor a first-degree relative with a psychotic disorder.

Our previous study in this cohort found no difference in reported symptoms between the siblings and healthy controls[100], allowing to combine both groups for the analysis. The exclusion criteria were poor command of the Dutch language, epilepsy, and intelligence quotient (IQ) < 75.

Ethical approval

This study was approved by the Medical Ethics Committee of the Leiden University Medical Center (NL37356.058.12/ P12.182). Written informed consent was obtained from all participants.

VR setting

The virtual environment used in this experiment was a cafe. Participants could navigate the virtual environment using a Logitech F310 Gamepad. The Sony HMZ-T1 head mounted display used for VR display of the cafe had a high-density resolution of 1280·720 (per eye), with 51.6 diagonal field of view, and built-in headphones. A 3DOF tracker (UM7 Orientation Sensor; CH-Robotics) was added to the Sony HMZ-T1 for head rotation. The researcher controlled the VR system and actions in the virtual environment using a graphical user interface. Detailed information on the conditions is already published[100]. The social stressors used in this virtual social environment (population density, ethnic density, and hostility) were found to elicit feelings of anxiety[100]. All participants participated in five conditions, each with different levels of social stress. Exposure to each condition lasted 4 min. The order of the five conditions was randomized to prevent a sequence effect.

Measurement instruments

Diagnostic instruments. The Comprehensive Assessment of At-Risk Mental States[61] was used to assess ARMS before participation. Psychotic disorder was diagnosed with either the Comprehensive Assessment of Symptoms and History[60] or the Schedules for Clinical Assessment in Neuropsychiatry[59]. Anxiety was assessed by self-rated momentary subjective fear in units on an analog scale (subjective unit of distress [SUD]), ranging from 0 (no distress at all) to 100 (worst possible distress). Anxiety was first assessed before the experiments. Participants also rated their maximum anxiety during VR immediately after each of the five experiments. The mean of these five maximum anxiety scores was calculated and used for the analyses. The self-report Simulator Sickness Questionnaire (SSQ)[141] was administered before and after the VR experiments. The SSQ measure's three distinct symptom clusters were labeled as Oculomotor (eyestrain,

difficulty focusing, blurred vision, headache), Disorientation (dizziness, vertigo), and Nausea (nausea, stomach awareness, increased salivation, burping). The SSQ was scored according to the procedures by Kennedy et al.[141].

Analyses

Analyses were conducted with IBM SPSS version 23. For sociodemographic characteristics, differences in continuous variables between the groups were analyzed using t tests. If the distribution of a continuous variable was skewed a Wilcoxon rank-sum test was used. Group differences in categorical variables were tested using v2 analysis. Pearson's correlation coefficient (two-tailed) was used for correlations. We used the MEMORE method[142] for two-condition within-participant statistical mediation analysis. The single test path-analytic approach by MEMORE eliminates the need for multiple discrete hypothesis tests about components of the mediation model, as the previous dominant approach[143] requires. A single test decreases the probability of an error occurring. The conditions were no exposure (baseline) and exposure to VR. MEMORE can be used to estimate the total (c), direct (c'), and indirect (ab) effects of exposure to VR on CS and its subscales through anxiety in a two-condition repeated measures design. Bootstrapping (5,000 samples) was used. Fixed covariates such as gender (or other stable individual differences) are accounted for in the MEMORE model.

Results

Demographics

A total of 170 participants were included: 95 controls in the low-liability group and 75 patients in the high-liability group. Sociodemographic characteristics of the participants as well as anxiety and CS scores are presented in table 4.1. Controls had a higher level of education and a lower use of psychiatric medication. There was a trend of more female participants in the control group.

Gender

At baseline, 90 percent of women and 86 percent of men reported at least one symptom of CS. Women reported more CS symptoms than men, both overall and for each CS subscale. These differences were present both before and after exposure to VR. No significant gender difference was found in the increase in total CS symptoms when exposed to VR (ranksum Z = 1.19; P = .24), or for oculomotor and disorientation separately. Women reported a stronger increase in nausea than men (rank sum Z = 2.31; P = .02) when exposed to VR. Results for both overall CS and for each of the three symptom categories separately are presented in figure 4.2. No differences were found between men and women in reported anxiety, either before or during exposure to VR.

Table 4.1. Characteristics of the study sample for all participants, for females and males separately, and for controls and patients separately

Characteristic	All participants (N = 170)	Female (N = 73)	Male (N = 97)	P	Controls (N = 95)	Patients (N = 75)	P
Sex female (n, %)	73 (42.9%)				47 (49.5%)	26 (34.7%)	.053
Age in years	25.4 (4.6)	24.7 (4.4)	25.9 (4.8)	.126	25.4 (4.6)	25.4 (4.7)	.943
Non-Dutch origin (n, %)	58 (34.3%)	27 (37.0%)	31 (32.0%)	.052	27 (28.7%)	31 (41.3%)	.078
Controls (n, %)	95 (55.9%)	47 (64.4%)	48 (49.5%)	.054			
Level of education (n, %)				.818			.002**
No/Primary	3 (1.8%)	1 (1.4%)	2 (2.1%)		0	3 (4%)	
Vocational ((V)MBO)	57 (33.7%)	22 (30.6%)	35 (36.1%)		24 (25.5%)	33 (44%)	
Higher Secondary (HAVO/VWO)	29 (17.2%)	12 (16.7%)	17 (17.5%)		14 (14.9%)	15 (20%)	
Higher Tertiary (HBO/University)	80 (47.3%)	37 (51.4%)	43 (44.3%)		56 (59.6%)	24 (32%)	
Medication use (n, %)				.038*			< .001**
None	112 (65.9%)	54 (74%)	59 (60.8%)		88 (92.6%)	24 (32%)	
Antipsychotic	35 (20.6%)	5 (6.9%)	19 (19.6%)		0 (0%)	35 (46.7%)	
Antidepressant	19 (11.2%)	7 (9.6%)	7 (7.2%)		2 (2.1%)	17 (22.7%)	
Benzodiazepine	10 (5.9%)	5 (6.9%)	3 (3.1%)		0 (0%)	10 (13.3%)	
Other	11 (6.5%)	2 (2.7%)	9 (9.3%)		4 (4.2%)	7 (9.3%)	
Anxiety before VR	21.3 (21.3)	22.2 (21.6)	20.7 (21.2)	.627	13.8 (14.1)	30.8 (24.9)	< .001**
Anxiety during VR	32.3 (24.7)	34.4 (24.9)	30.7 (24.5)	.252	24.0 (18.8)	42.8 (27.2)	< .001**
Cybersickness total before VR	32.7 (37.7)	42.3 (44.2)	25.6 (30.4)	.011*	20.6 (26.8)	47.9 (43.7)	< .001**
Cybersickness total after VR	46.7 (38.7)	61.4 (41.4)	35.7 (32.6)	< .001**	44.9 (39.3)	49.0 (38.0)	.377
Oculomotor before VR	32.7 (33.3)	42.1 (37.6)	25.6 (27.6)	.004**	22.6 (26.7)	45.5 (36.3)	< .001**
Oculomotor after VR	33.3 (30.6)	43.7 (33.9)	25.4 (25.4)	< .001**	29.3 (29.3)	38.3 (31.6)	.034*
Nausea before VR	23.3 (29.2)	28.0 (33.2)	19.6 (25.2)	.121	12.3 (18.1)	37.0 (34.6)	< .001**
Nausea after VR	40.3 (36.1)	52.5 (36.8)	31.1(32.7)	< .001**	40.6 (37.4)	39.9 (34.5)	.955
Disorientation before VR	27.8 (46.5)	38.4 (56. 8)	19.7 (34.7)	.008**	17.5 (34.0)	40.6 (56.1)	.001**
Disorientation after VR	54.0 (51.9)	71.5 (58.7)	40.6 (41.7)	< .001**	54.2 (52.1)	53.6 (51.9)	.970

Note. Values are presented as mean (standard deviation) or n (%). VR = virtual reality. Cybersickness was measured by the self-report Simulator Sickness Questionnaire (SSQ). Anxiety was assessed by self-rated momentary subjective fear (SUD 0–100). Group differences between controls and patients of continuous variables were analyzed using a t-test, or Wilcoxon's rank sum if skewed. Group differences of categorical variables were analyzed with chi2. * P < .05. ** P < .01.

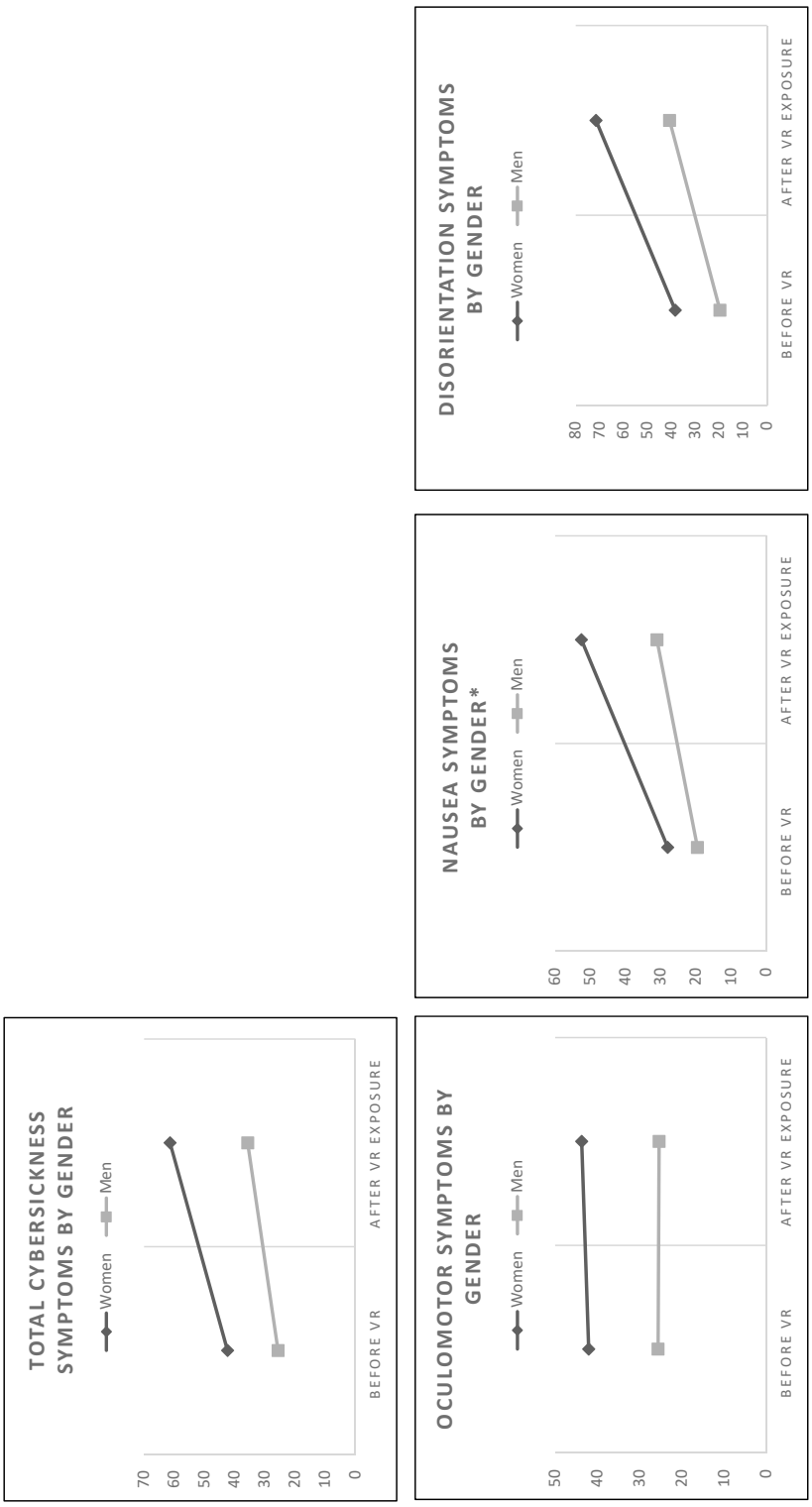

Figure 4.2. By gender, cybersickness symptoms before and after exposure to virtual reality.
Note. VR = Virtual Reality. * P < .05; Women show a significantly steeper increase in nausea symptoms when exposed to VR compared to men.

Patients and controls

At baseline, 81 percent of the controls and 96 percent of the patients reported at least one symptom of CS. Patients reported significantly more symptoms of CS at baseline than the controls. After exposure to VR, there was no significant difference in nausea and disorientation between the two groups. Results for both overall CS and for each of the three symptom categories separately are presented in figure 4.3. At baseline, there was a significant correlation between anxiety and CS for patients (r = .33, P < .01), whereas this was not found for the controls (r = -.03, P = .74). In contrast, after exposure to VR, patients no longer showed a significant correlation between anxiety and CS (r = .19, P = .11), whereas the controls did (r = .53, P < .01).

Anxiety as mediator variable

For all 170 participants, a significant correlation was found between anxiety and CS at baseline (r = .33, P < .01) and after exposure to VR (r = .34, P < .01). Mediation results are presented in table 4.2. Anxiety mediated the relationship between exposure to a VR environment and the experience of CS. The direct effect (c') remained significant, implying that the mediation effect of anxiety on CS was partial. Examination of the CS subscales revealed that the relationship between exposure to VR and nausea was partially mediated by anxiety. The relationship between exposure to VR and disorientation was

Table 4.2. Effect of the mediator variable 'anxiety' on the relationship between Virtual Reality exposure and cybersickness, both overall and for each of its three subscales in all participants (n = 170)

	Effect	SD	P	CI [95%]	
Cybersickness total					
Total effect (*c*)	-13.77	2.87	< .001**	-19.44	-8.08
Direct effect (*c'*)	-9.13	3.40	.008**	-15.85	-2.41
Indirect effect (*ab*)	-4.64	2.11	.018[a]*	-9.06	-.79
Oculomotor					
Total effect (*c*)	-.58	2.15	.787	-4.82	3.66
Nausea					
Total effect (*c*)	-17.10	3.01	< .001**	-23.05	-11.15
Direct effect (*c'*)	-11.73	3.55	.001**	-18.74	-4.73
Indirect effect (*ab*)	-5.37	2.20	.009[a]**	-10.22	-1.43
Disorientation					
Total effect (*c*)	-26.26	3.83	< .001**	-33.84	-18.69
Direct effect (*c'*)	-20.45	4.56	< .001**	-29.45	-11.44
Indirect effect (*ab*)	-5.82	2.96	.027[a]*	-12.12	-.41

Notes. SD = standard deviation; [a] Sobel test was used to estimate P-value of indirect effects. Cybersickness was measured by the self-report Simulator Sickness Questionnaire (SSQ). Anxiety was assessed by self-rated momentary subjective fear (SUD). MEMORE was used for two-condition within-participant statistical mediation analysis. The conditions were no exposure (baseline) and exposure to virtual reality. Fixed covariates, such as gender, are accounted for in the MEMORE model.* < .05. ** < .01.

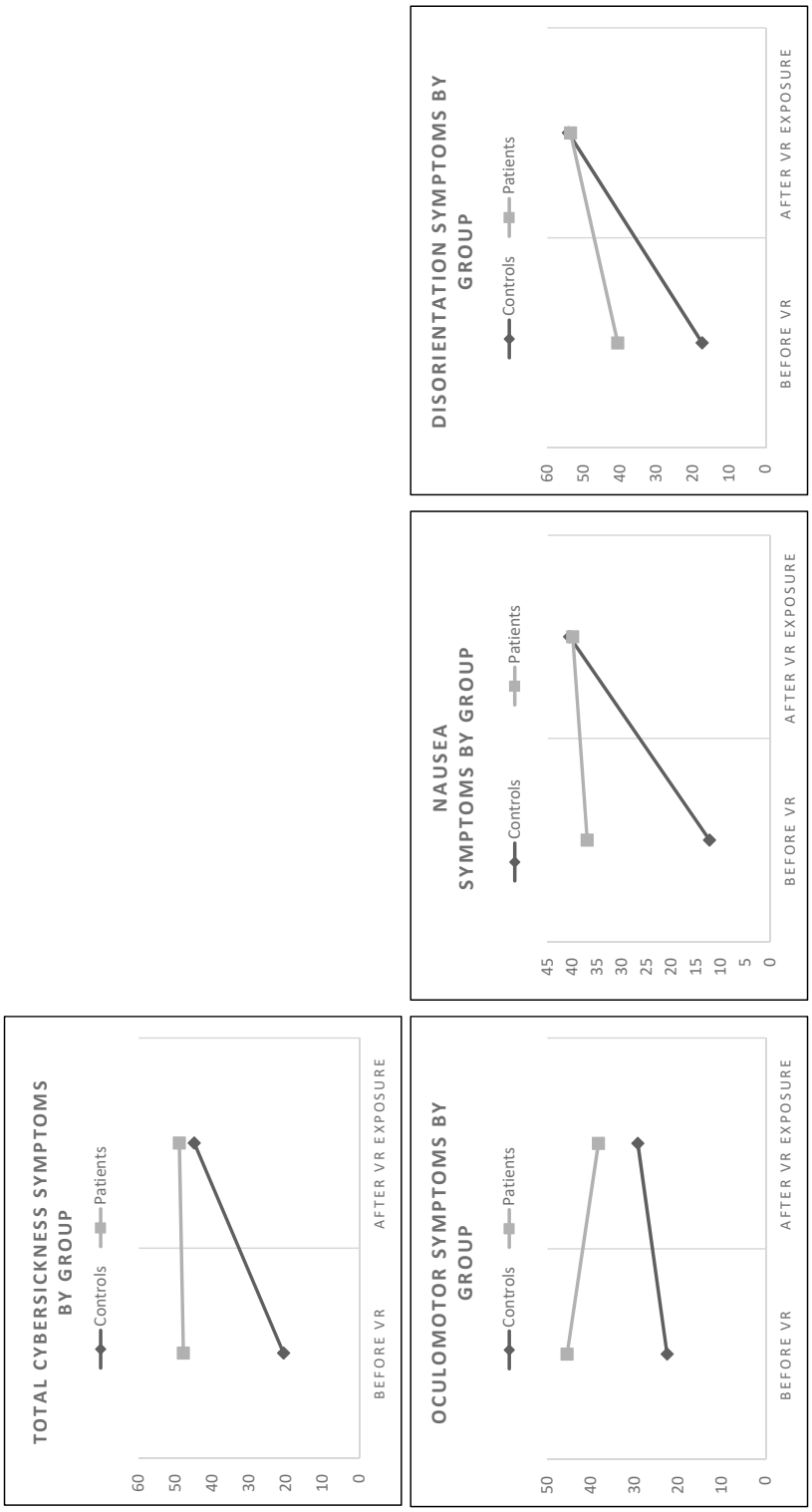

Figure 4.3. By group, CS symptoms before and after exposure to VR.
Note. VR = Virtual Reality.

also partially mediated by anxiety. Oculomotor symptoms had no direct relationship (c) with exposure to VR.

Discussion

In this VR study, the large majority of patients and controls reported at least one symptom of CS. We replicated both gender differences in CS and differences in CS between patients and controls. The relationship between exposure to VR and CS was partially mediated by anxiety. This implies that part of the relationship between exposure to VR and CS symptoms, more specifically nausea and disorientation, was explained by anxiety as an intermediary variable. Women reported more CS symptoms than men, but most of these differences were already present at baseline. When exposed to VR, women had a steeper increase in nausea symptoms. The gender difference in severity of CS symptoms is in accordance with others[132]. However, gender differences in oculomotor and disorientation symptoms existed before VR exposure and cannot be explained by either exposure to VR or anxiety levels. Our results replicate both findings about CS symptoms being present before exposure to VR in patients with an anxiety disorder[138], and associations found between anxiety and CS symptoms[139,140]. Our results replicate findings that significant correlations between anxiety and CS were found in controls[136] but not in patients[137,138]. Our study indicates that a partial explanation may lie in a ceiling effect for CS symptoms, that is, CS symptoms were already high in patients before VR and remained high, whereas they were low in healthy controls before VR and increased during VR. A second explanation may be the partial overlap between CS symptoms and physiological anxiety responses. CS symptoms reported at baseline cannot be explained by exposure to VR, but are related to anxiety. The present study found that anxiety was a mediating factor for nausea and disorientation symptoms of CS, but not oculomotor symptoms.

This suggests that anxiety may impact some, but not all symptoms of CS. This is in line with studies showing five individual symptoms of CS (general discomfort, fatigue, headache, difficulty concentrating, and fullness of head) to correlate with reported anxiety[139,140]. Especially two CS symptoms, general discomfort and difficulty concentrating, may reflect anxiety symptoms as they significantly load on the anxiety factor[140]. This is also in line with a study demonstrating that nausea symptoms are affected by reported anxiety[134]. We found no increase in oculomotor symptoms after exposure to VR; previous research on the profile of CS found that oculomotor symptoms are the least likely to occur[144], which may have influenced the statistical power. It is also possible that oculomotor symptoms (e.g., eyestrain and blurred vision) are physiologically less related to anxiety symptoms. The fact that mediation by anxiety is partial and is consistent with the finding that multiple factors influence CS[128].

Strengths and limitations

The primary strength of the study is that the CS symptoms were measured before and after exposure to VR. Also, three different CS subscales were measured instead of only nausea, or using a single-sickness scale. Second strength is that the inclusion of both patients and controls allowed examining group differences. Thirdly, the MEMORE method simultaneously used the CS and anxiety scores before exposure to VR, as well as scores after exposure, to estimate mediation effects. On the contrary, the statistical power of this study was limited, as many participants reported little CS and little or no anxiety symptoms; this impeded more detailed analysis of the subgroups. Four of the SSQ items load on two subscales instead of one, which inflate the contribution of these items on the total score. As two of these items, general discomfort and difficulty concentrating, are known to be correlated with anxiety[140], this might have affected analysis. Only two specific patient groups were included and all participants were relatively young; both these factors limit the generalizability of our findings. Also, this study examined state anxiety only, whereas additional affect states should be explored in future research. As a stable individual difference trait, anxiety is accounted for in the MEMORE model. However, as it can influence both the anxiety response and the CS symptoms, more research is required to clarify its potential role. Another limitation is that anxiety was measured with self-report. Finally, this study used the diagnostic criteria of the DSM-IV instead of the current DSM-V; however, as there are only marginal differences in the categories of psychotic disorders[145] the effect on the individual diagnosis of each patient in the present study can be considered negligible.

Clinical implications and future directions

This study indicates that caution is required when interpreting studies on both CS and anxiety, until the specificity in measurements has been improved. Gender differences in CS should also be taken into account. Findings on CS based on controls cannot be generalized to patients. Reported anxiety symptoms may partially reflect CS symptoms and vice versa. The relationship between VR exposure and CS symptoms is partially explained by anxiety as an intermediary variable. When VR therapy reduces anxiety, the nausea and disorientation symptoms are expected to decline. In addition, CS symptoms decrease after repetitive use of VR[146]. If a patient reports anxiety and CS during the first stages of VR treatment and can tolerate this, we recommend to continue with VR treatment. Future research should include patients diagnosed with an anxiety disorder, and measure both state and trait anxiety. Replication with a larger sample size of a broad age range is necessary to be able to perform more detailed analysis of subgroups and further clarify mechanisms.

5

Chapter 5

Effect of Virtual Reality Exposure Therapy on social participation in people with a psychotic disorder (VRETp): Study protocol for a randomized controlled trial

Roos Pot-Kolder · Wim Veling ·
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Abstract

Background: Many patients with a psychotic disorder participate poorly in society. When psychotic disorders are in partial remission, feelings of paranoia, delusions of reference, social anxiety and self-stigmatization often remain at diminished severity and may lead to avoidance of places and people. Virtual reality exposure therapy (VRET) is an evidence-based treatment for several anxiety disorders. For patients with a psychotic disorder, the VRETp was developed to help them experience exposure to feared social situations. The present study aims to investigate the effects of VRETp on social participation in real life among patients with a psychotic disorder.

Methods/Design: The study is a single-blind randomized controlled trial with two conditions: the active condition in which participants receive the virtual reality treatment together with treatment as usual (TAU), and the waiting list condition in which participants receive TAU only. The two groups are compared at baseline, at 3-months posttreatment and at 6-months follow-up. All participants on the waiting list are also offered the virtual reality treatment after the follow-up measurements are completed. The primary outcome is social participation. Secondary outcomes are quality of life, interaction anxiety, depression and social functioning in general. Moderator and mediator analyses are conducted with stigma, cognitive schemata, cognitive biases, medication adherence, simulator sickness and presence in virtual reality. If effective, a cost-effectiveness analysis will be conducted.

Discussion: Results from the posttreatment measurement can be considered strong empirical indicators of the effectiveness of VRETp. The 6-month follow-up data may provide reliable documentation of the long-term effects of the treatment on the outcome variables. Data from pre-treatment and mid-treatment can be used to reveal possible pathways of change.

Trial registration: Current Controlled Trials: ISRCTN12929657
http://www.isrctn.com/ISRCTN12929657

Background

A large number of patients with a psychotic disorder participate poorly in society, even if their psychotic symptoms have been treated successfully. Unemployment is high at 80–85%[147] and about 75% does not have a relationship with a partner[148]. A study comparing the social network of young people with early psychosis and matched controls, showed that the psychosis group had smaller networks, fewer friends, fewer people to turn to in a crisis, and a greater likelihood of service providers as members[149]. Social network size is also associated with the likelihood of in-patient treatment and with the number of services used by psychotic patients[150]. Social isolation hinders patients in multiple areas of functioning, such as developing and maintaining a social network, the ability to function in work-related environments, and even in performing daily tasks needed for independent living (e.g. shopping for groceries). When psychotic disorders are in partial remission, the remaining feelings of paranoia and delusions of reference often cause patients to avoid places and people. Moreover, this conditioned avoidance does not improve with antipsychotic medication[151].

Exposure

The evidence-based psychological treatment for experiencing fear and paranoia in social situations is cognitive behavioral therapy (CBT) with exposure in vivo, such as the therapist taking a patient shopping or exposing the patient to public transportation. This form of treatment in vivo has several limitations. First, the social world in which in vivo exposure takes place cannot be experimentally manipulated. Second, exposure therapy in vivo is costly and not readily available in most mental healthcare institutes. Thirdly, therapy sessions are used to prepare exposure exercises, which the patient is expected to perform between sessions; however, even with careful tailoring to the patients' capabilities, it is often difficult for patients to do these exercises as planned. Fourthly, not all patients tolerate exposure in vivo.

Anxiety disorders and VRET

Virtual reality exposure therapy (VRET) is an evidence-based treatment for several anxiety disorders[152]. It has the potential to be an affordable and accessible form of treatment to enhance social participation and wellbeing for patients suffering from a psychotic disorder and social withdrawal. In virtual worlds fear is experienced similar to the in vivo experience. It is the experience of being there (known as 'presence') which the three-dimensional virtual reality (VR) environment creates, together with a narrative about the environment, that enables people to feel and behave as they would in real life. This principle makes it possible to overcome fear and practice new behavior in a virtual environment[153]. An advantage of VR is that people find it easier to start exposure, since they know there is no real threat to their safety[154]. In students suffering from fear of

spiders, 81–89% chose VR exposure over in vivo exposure[155]. A study comparing VR exposure vs. in vivo exposure in specific phobias showed that 76% of the patients chose VR exposure over in vivo exposure[156]. The refusal rate for in vivo exposure (27%) was higher than that for the VRET (3%). In total, 90.4% of the patients that preferred VR exposure said they did so because they were too afraid to confront the real situation or to object. These results suggest that the availability of VR exposure may increase the number of patients who are willing to engage in exposure-based therapy.

VRET in psychosis

In a VRET treatment protocol, patients are gradually exposed to controlled social environments that induce fear and in which individually-tailored exposure exercises can be designed. The ability to provide fear-inducing VR social environments is partially dependent on the availability of anxiety-provoking stimuli in the software of the virtual worlds. The present study will assess whether the currently used anxiety-provoking stimuli sufficiently match the stimuli asked for by patients during treatment.

An experimental virtual world was developed. The ecological validity of the VR environment has been demonstrated. For patients suffering from psychosis a significant correlation was found between paranoia and social interaction anxiety in real life and paranoid thoughts about the avatars in the VR world[62]. A higher degree of paranoia was found when more avatars were present, when avatars had hostile facial expressions, and when more of the avatars had a different ethnicity[157].

Preliminary findings using VRET with psychosis show that patients experiencing paranoia are willing to participate in VR environments, that they report paranoid thoughts about the virtual people (avatars), but at the same time are willing to confront the fearful situation[62,158]. Social virtual environments have the potential to enhance CBT by helping patients recovering from psychosis to understand the role of avoidance and safety behaviors in the maintenance of interaction anxiety and paranoia. Additionally, it can enhance their confidence to carry out real-life behavioral experiments[159].

Side-effects and safety

A phenomenon called simulator sickness (also known as cyber sickness) can occur when using VR applications. Symptoms are similar to those of motion-induced sickness, but tend to be less severe and have a lower incidence[160]. It is suggested that simulator sickness sensations can be at least partially explained by an overlap with anxiety symptoms[10]. A pilot study on Virtual Reality and Psychosis showed low symptoms of simulator sickness, and no significant increase between pre- and post-measurement[62]. Since simulator sickness is known to increase with the duration of exposure[161], measurement of these symptoms will be included in the study protocol.

No adverse effects were found in studies using VR to expose psychotic patients to virtual social environments. A study with 20 psychotic patients diagnosed with first-episode psychosis experiencing at least moderate paranoia found that VR did not lead to more anxiety or physical complaints directly after the experiments; follow-up one week later showed that no patients reported an increase in intrusive negative thoughts, unpleasant emotions or behavioral changes as a consequence of the VR experience[10]. Similar results were found in a study of 21 patients with at-risk mental state for psychosis[154]. Our own pilot study confirmed that patients did not become more psychotic as a result of exposure to our virtual social environment[62].

Objectives

As this is a new form of treatment for social withdrawal in psychosis, the first step is to demonstrate the effect of VRET compared to a waiting list condition on social participation in real life. Objective social participation is defined as the time spent in social situations with other people and the time spent interacting with other people in everyday life. Subjective social participation is how patients experience these social situations; this experience is expressed as momentary paranoia, perceived social threat and event stress, as experienced in situations with other people.

We hypothesize that, after applying the intervention for patients suffering from paranoia (VRETp), they will show improved social participation.

Primary objective
To determine the effectiveness of VRETp in patients with psychosis, defined as improved social participation.

Hypothesis 1: The amount of time spent with other people will increase, as measured 60 times a week in real life.

Hypothesis 2: Momentary paranoia, perceived social threat and event stress as experienced in social situations will decline, as measured 60 times a week in real life.

Secondary objectives
Secondary objectives are to investigate:

a) the acceptability of VRETp for patients and therapists
b) the effects on interaction anxiety, depression, quality of life and social functioning in general

c) the moderating and mediating effects of stigma, schemata about the self and others, cognitive biases, medication adherence, simulator sickness and experienced presence in the VR environment
d) the cost-effectiveness of VRETp

Methods

Participants

Included are patients diagnosed with a psychotic disorder at seven mental health institutions in the Netherlands: a list of study sites can be obtained from the corresponding author. Written Informed consent is obtained from each participant.

Inclusion criteria

To be eligible to participate, patients must meet all of the following criteria:

- DSM IV diagnosis of a psychotic disorder according to the MINI.
- Avoiding either shops, streets, public transportation or bars/restaurants as assessed by the Safety Behavior Questionnaire (SBQ).
- A paranoia score (> 40) as assessed by the Green Paranoid Thoughts Scale (GPTS)
- Age 18–65 years

Exclusion criteria

- IQ ≤ 70. IQ must be established by a valid instrument, such as the WAIS of WISC. Information on IQ can be found in the status chart of the patient. In case of doubt, the short form of the WAIS III is used to assess IQ
- Insufficient command of the Dutch language
- Epilepsy. If no epilepsy is mentioned in the patient status, this is checked with the patient.

Measurement instruments

Social participation (primary outcome)

Social participation is measured with the PsyMate experience sampling device. This form of Experience Sampling Measurement (ESM) has high ecological validity[162]. ESM is a self-assessment technique using random time sampling, and has the advantage that it can assess mental state and social context in everyday life as it occurs. Because the ESM assesses 'at the moment' it is less vulnerable for recall bias and a valuable instrument

to assess clinical phenomena in the real world[163]. ESM is effective for patients with a psychotic disorder with current symptoms, as well as for patients with a psychotic disorder in remission164. A review of studies using the ESM it to be valid for measuring situational characteristics, such as social environment[30]. Event stress, social environment and company (time spent in company with others and the kind of company) are operationalized in accordance with the work of Collip et al.[164]. Research on the (social) context of delusions in schizophrenia shows the ESM to be a valid aid in collecting data of daily life social situations[165]. Momentary paranoia, using four established ESM items, is a valid measure to assess state paranoia[166]. Perceived social threat, using four established ESM items, is a valid measure to assess perceived social threat as a more subtle indicator of paranoia[164].

Eligibility measurements

Psychotic disorders

The MINI-Plus interview is used for diagnosing lifetime psychotic disorders. This interview provides a reliable DSM diagnosis for psychotic disorders. The good psychometric characteristics of the MINI (-Plus) make it a good choice for research purposes[167-169].

Paranoid thoughts

Paranoia symptoms are assessed with the GPTS[170]. The GPTS consists of 32 items divided into two 16-item scales, assessing ideas of social reference and persecution. Good internal consistency and validity are established for both of the scales and their dimensions[170].

Safety behavior

The Safety Behavior Questionnaire – persecutory delusions (SBQ) is used to assess safety behaviors (such as avoidance) for social situations[171]. An action was considered to be safety behavior if the patient reported that it had been carried out with the aim to reduce a persecutory threat. The patient was asked to rate the frequency of the safety behavior over the last month on a 4-point scale. Psychometric properties of the SBQ range from poor to excellent[171].

Secondary outcome measures

Quality of life

The Manchester Short Assessment of Quality of Life (MANSA) is a brief instrument used to assess quality of life, focusing on satisfaction with life as a whole and with life domains. Its psychometric properties are satisfactory[172].

Interaction anxiety

Interaction anxiety symptoms were assessed with the Social Interaction Anxiety Scale (SIAS)[173]. The SIAS consists of 19 items that assess the tendency to fear and avoid social situations. Responses can range from 0 (not at all) to 4 (extremely). The SIAS has good psychometric properties[173,174].

Social functioning

The Social and Occupational Functioning Assessment Scale (SOFAS) is used to subjectively assess and rate social and occupational functioning, but not psychological symptoms[175,176].

Depression

The Beck Depression Inventory (BDI-II) consists of 21 items assessing symptoms and level of depression over the past two weeks. The BDI-II is a psychometrically sound instrument[177].

Moderators and mediators

Stigma

The Internalized Stigma of Mental Illness (ISMI) is a 29-item questionnaire that measures self-stigma among persons with psychiatric disorders. The ISMI shows reliability and validity[178].

Schemata

Schemata of self and others (BCSS) has 24 items concerning beliefs about the self and others that are assessed on a 5-point rating scale (0–4). The BCSS has good psychometric properties[179].

Cognitive biases

The Davos Assessment of Cognitive Biases Scale (DACOBS) has seven independent subscales each with six items; jumping to conclusions, belief inflexibility bias, attention for threat bias, external attribution bias, social cognition problems, subjective cognitive problems and safety behavior. The DACOBS is reliable and valid for use in clinical practice and research[180].

Medication adherence

The Brief Adherence Rating Scale (BARS) is an instrument used to assess the antipsychotic medication adherence of patients with a psychotic disorder. The BARS consists of four items: three questions and an overall visual analog rating scale to assess the proportion of doses taken by the patient in the past month (0%–100%). The psychometric properties are adequate[181].

Participants and their psychiatrists are asked not to change any medication during the trial.

Simulator sickness

The Simulator Sickness Questionnaire (SSQ) was developed to accommodate symptoms specific to simulator technology. The SSQ requires the user to report the subjective severity of symptoms such as general discomfort, headache, eyestrain and fatigue[160]. Although its psychometric properties are adequate, there is room for improvement[182].

Presence

The Igroup Presence Questionnaire (IPQ) consists of 14 items assessing sense of presence in virtual environments. Responses are made on a 7-point Likert scale. The IPQ has demonstrated good psychometric properties[183].

Cost-effectiveness

The Trimbos/iMTA questionnaire for costs associated with psychiatric Illness (the TiC-P) is designed for self-report by patients with a mental disorder. The questionnaire focuses on establishing direct medical costs and productivity costs during paid or unpaid work. The psychometric properties are reported to be adequate[184].

Design

The study is a single blind randomized controlled trial (RCT) with two conditions: i) the active condition in which subjects receive the VR treatment besides treatments as usual (TAU) and ii) the waiting list condition during which subjects receive TAU only. All participants on the waiting list are also offered the VR treatment after follow-up measurements have been completed. The two groups are compared at baseline, at 3 months post treatment and at 6 months follow-up. The waiting list condition receives the VRET treatment after 6 months. An overview of measurements can be found in Table 5.1.

Power and sample size calculation

In this RCT, the effect of VRETp on social participation is investigated by comparing this treatment with a waiting list condition. Social participation is assessed with the PsyMate experience sampling method (ESM; see Measurements). Self-assessments are rated on a 7-point Likert scale. Main outcome items are social environment and company, perceived social threat in company, event stress, and momentary paranoia. Estimated mean scores and standard deviations (SD) are not readily available because there are no previous VRETp studies with psychotic patients.

Table 5.1. Characteristics of study sample

Outcome	Measurement Interview (i) Self-report (s)	T0 Baseline	T1 Session 4	T2 Session 8	T3 Post treatment	T6 Follow-up
Social participation	Experience Sampling Method (s)	x			x	x
Paranoia	GPTS (s)	x	x	x	x	x
Interaction anxiety	SIAS (s)	x	x	x	x	x
Depression	BDI-II (s)	x			x	x
Stigma	ISMI (s)	x			x	x
schemas	BCSS (s)	x			x	x
Safety behavior	SBQ (i)	x			x	x
Cognitive biases	DACOBS (s)	x			x	x
Social functioning	SOFAS (i)	x			x	x
Quality of life	MANSA (i)	x			x	x
Cost-effectiveness	TIC-P (i)	x			x	x
Cyber sickness	SSQ (s)		x	x		
Presence	IPQ (s)		x	x		
Medication adherence	BARS (i)	x	x	x	x	x

Using an estimated (moderate) effect size of 0.5 with a power of 0.8, an alpha of 0.05 and a two-sided independent t-test, yields n = 64 in each group. Therefore, at least 64 participants need to be included in each arm (total n = 128 patients). As attrition is estimated at about 20%, 80 participants need to be included in each condition (total n = 160 patients).

Procedure

Patients with a chart diagnosis of schizophrenia, schizophreniform disorder, schizo-affective disorder, delusional disorder or psychotic disorder NOS, will be informed about the study by their treating specialist and asked to participate. Each patient is asked for written permission to be contacted by the researchers if eligible for VRETp. If eligible, the treating specialist discusses participation of the patient in the study with the remainder of the team and gives permission to the researchers to contact the patient. When permission is given, additional information is provided and patients have two weeks to consider whether they really wish to participate. The VRETp treatment is additional to current treatment and declining to participate has no negative consequences at all for patients. For each of the participating organizations an independent specialist is available for patients to contact. Contact information of this specialist is available in the information letter given to the patients of the participating organizations.

Informed consent from all participants is obtained before assessment by the researcher. The MINI-Plus interview is used to diagnose psychotic disorders. Patients who are

willing to participate are screened for avoidance behavior (SBQ) and for paranoia using the GPTS (cut-off > 40)[63]. Baseline measurements are obtained. Randomization is used to allocate a patient to either the VRETP or to the waiting list condition. Patients allocated to the VRETp group start their treatment, which consists of a maximum of 16 sessions with a maximum duration of 60 min each.

At baseline (T0) the research assistant assesses the baseline measurement of all primary and secondary variables. At two weeks (T1) and four weeks (T2) into treatment, respectively, participants in the treatment condition are assessed for their scores on paranoia, interaction anxiety, cyber sickness, presence in the virtual world and medication adherence, using self-report questionnaires handed out by the therapist, or interview questions (medication adherence).

At the end of treatment (T3) and at follow-up (T6), the research assistant assesses the primary and secondary measures. The flow diagram can be seen in Figure 5.1.

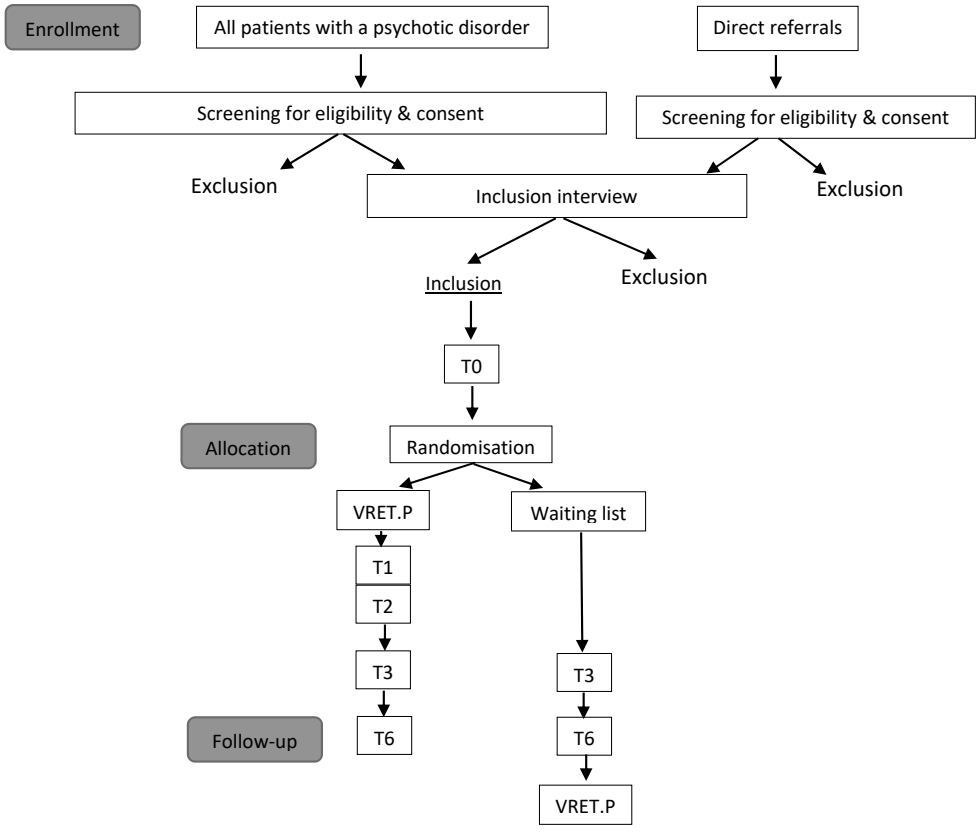

Figure 5.1. Flow diagram VRETP.
Note. TAU = Treatment as usual.

Randomization

A block of 12 random assignments will be made for each participating mental health center. Each block has 6 assignments for each condition: VRETp or waiting list. If a center includes more patients, new blocks of 12 random assignments will be made available. The blocks are made using a scientific randomization program (www.randomizer.org) by the independent randomization bureau of Parnassia Psychiatric Institute. Participants and therapists are informed about the randomization by mail and e-mail, respectively.

Interventions

Participants in both the VRETp and the waiting list condition receive TAU, consisting of antipsychotic medication, and treatment and/or supportive counseling by therapists, caseworkers or coaches. TAU is considered to be equal in both conditions as a result of the randomization procedure used (see Randomization). During the trial participants are not allowed to receive any therapy aimed at improving social participation.

Virtual reality exposure therapy (VRET)

VRETp treatment has a maximum of 16 treatment sessions of 60 min each. This number of sessions is somewhat larger than is usual for CBT in anxiety disorders. Our rationale for this is our expectation that treating paranoia requires more time compared with treating regular anxiety. People suffering from a psychotic disorder often show severity and durance in their social avoidance. Negative symptoms make it difficult to motivate people for therapy and this is a continuing process during treatment. The treatment protocol states that the therapists receive 16 h of training; all therapy sessions are recorded. A selection of the sessions is rated for treatment fidelity using the Cognitive Therapy Rating Scale (CTRS). The CTRS is a reliable[185] and valid[186] instrument to measure treatment fidelity when following a CBT protocol. Monthly 4-h group supervision serves to guide the therapists throughout the intervention period.

Existing CBT protocols will be adapted for VRET treatment in one area: exposure in vivo will be replaced by VR exposure. The remainder of the treatment protocol consists of well-known, evidence-based CBT elements, e.g. providing treatment rationale, behavioral experiments, reducing safety behavior, and attention training. Starting with exposure exercises for social situations which are lowest in the patient's anxiety hierarchy, the exposure exercises take place during the therapy session using the Virtual Reality system. Participants are not allowed to receive any other form of therapy aimed at improving social participation during the trial. At all times the therapist is in control of the VRETp intervention and is able to immediately change/stop the virtual environment if necessary.

Early completions
A participant is considered an early completer of treatment when the subjective units of distress on a scale of 0 (no stress at all) to 100 (extremely stressful) in all the virtual situations that are part of the case conceptualization are reduced to zero in two consecutive sessions. This criteria is restrictive and was chosen to prevent therapies being ended prematurely, since no point of reference has been established for treating paranoia using VR exposure.

Discontinuation
Participation is completely voluntary and participants can withdraw from participation at any time for any reason. Participants who drop-out or otherwise deviate from the intervention protocol are requested to continue to participate in the measurements.

Fidelity checks
Audiotapes are made of all sessions and a selection of them is rated for treatment fidelity. All therapists are supervised by a highly skilled professional (MvdG) to evaluate, guide and approve the case conceptualization. Every six weeks, 4-h group supervision supports the therapist for the duration of the intervention. By means of a questionnaire, for each session the therapist reports on the elements and steps in the treatment protocol. Any deviation from the protocol is reported to the supervisor.

Unblinding
The study is single-blinded, meaning that research assistants who do the measurements are kept blinded regarding randomization of the participants. Participants are regularly instructed not to tell the research assistants which group they are allocated to; if a research assistant is accidentally unblinded during a measurement, that measurement is stopped. A new appointment is then made with another blinded research assistant.

Adverse events
The rules and regulations of the Medical Ethics Committee concerning adverse events are followed. All participants are insured in case any harm is caused related to trial participation.

Analyses

Data management
All data are directly coded with a number. Data and personal information of the participants are kept separately and safely stored to ensure privacy. All data entry is

double-checked. A data monitor from Parnassia Psychiatric Institute is appointed for the study.

Data analysis
Multilevel linear mixed modeling is used to analyze the data according to the intention-to-treat principle. Completer analysis is conducted with ANCOVA. Moderator and mediator analysis are conducted to assess the effects of moderators and mediators. Cost-effectiveness is conducted with social participation as the outcome.

Ethics
Ethical approval of the protocol was granted by 'De Medisch Ethische Toetsingscommissie VU medisch centrum' (METC number: NL37356.058.12).

Discussion

The main goal of the study is to investigate the effect of VRETp on improving social participation in patients with psychosis in real life. We hypothesize that VRETp will increase social participation objectively (time spent in company) and subjectively (experience less anxiety and paranoia during in social situations). Comparison between VRETp treatment and a waiting list condition will provide information about the effectiveness of VR exposure therapy for this population. This should make an important contribution to treatment options for people suffering from psychosis and social isolation. Improving social participation is of great personal value to patients with psychosis who suffer from the consequences of avoiding social situations in daily life.

In addition to social participation, the effect of VRETp on psychological, emotional and social well-being, especially paranoia and Interaction anxiety, is explored. Studying these variables may help disentangle the complex phenomena related to social participation in patients with psychosis.

Another aspect of the study is cost-effectiveness. If social participation improves it is expected that patients will become more independent, consume less care and, thereby, diminish costs related to extended health care.

Abbreviations
BARS: Brief Adherence Rating Scale; BCSS: Brief Core Schema Scales; BDI-II: Beck Depression Inventory; CBT: Cognitive Behavioral Therapy; CTRS: Cognitive Therapy Rating Scale; BACOBS: Davos Assessment of Cognitive Biases Scale, ESM: Experience Sampling Measurement; GPTS: Green et al. Paranoid Thought Scales; IC:

Informed Consent; IPQ: Igroup Presence Questionnaire; ISMI: Internalized Stigma of Mental Illness; MANSA: Manchester Short Assessment of Quality of life; MINI: Mini International Neuropsychiatric Interview; SBQ: Safety Behavior Questionnaire – persecutory delusions, SIAS: Social Interaction Anxiety Scale; SOFAS: Social and Occupational Functioning Assessment Scale; SSQ: Simulator Sickness Questionnaire; TiC-P: Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness, VR: virtual reality; VRET: Virtual Reality Exposure Therapy.

6

Chapter 6

Virtual-reality-based cognitive behavioral therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: A single-blind randomised controlled trial

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Abstract

Background: Many patients with psychotic disorders have persistent paranoid ideation and avoid social situations because of suspiciousness and anxiety. We investigated the effects of virtual-reality-based cognitive behavioral therapy (VR-CBT) on paranoid thoughts and social participation.

Methods: In this randomized controlled trial at seven Dutch mental health centers, outpatients aged 18–65 years with a DSM-IV-diagnosed psychotic disorder and paranoid ideation in the past month were randomly assigned (1:1) via block randomization to VR-CBT (in addition to treatment as usual) or the waiting list control group (treatment as usual). VR-CBT consisted of 16 individual therapy sessions (each 1 h long). Assessments were done at baseline, after treatment (i.e., 3 months from baseline), and at a 6-month follow-up visit. The primary outcome was social participation, which we operationalized as the amount of time spent with other people, momentary paranoia, perceived social threat, and momentary anxiety. Analysis was by intention to treat. This trial was retrospectively registered with ISRCTN, number 12929657.

Findings: Between April 1, 2014, and Dec 31, 2015, 116 patients with a psychotic disorder were randomly assigned, 58 to the VR-CBT group and 58 to the waiting list control group. Compared with the control, VR-CBT did not significantly increase the amount of time spent with other people at the post-treatment assessment. Momentary paranoid ideation (b = -0.331 [95% CI -0.432 to -0.230], P < .0001; effect size -1.49) and momentary anxiety (-0.288 [-0.438 to -0.1394]; P = .0002; -0.75) were significantly reduced in the VR-CBT group compared with the control group at the post-treatment assessment, and these improvements were maintained at the follow-up assessment. Safety behavior and social cognition problems were mediators of change in paranoid ideation. No adverse events were reported relating to the therapy or assessments.

Interpretation: Our results suggest that the addition of VR-CBT to standard treatment can reduce paranoid ideation and momentary anxiety in patients with a psychotic disorder.

Introduction

People with psychotic disorders often avoid public and social activities. Their social networks are generally small and they spend more time alone than people without a psychotic disorder[24]. Many people with psychotic disorders do not have romantic partners, and the unemployment rate is high[25,26]. As many as 90% of patients have paranoid ideation to some degree[18]. Often, such ideation is strong and manifests as paranoid delusions, which are characterized by unfounded anticipation of intentional harm inflicted by other people. The anxiety resulting from paranoid ideation strongly contributes to social avoidance. This conditioned avoidance is not always affected by use of antipsychotic medication[18]. Cognitive behavioral therapy (CBT) is the most effective psychological treatment for people with psychotic disorders[187]. The effect sizes of CBT on paranoid delusions and social functioning are small to medium, but can be improved by more emphasis on behavioral rather than cognitive change, and by more person-specific exposure[187]—a key element of CBT. Exposure-based therapeutic exercises for paranoid ideation have several limitations. First, the social environment and reactions of others cannot be controlled by the therapist—relevant events might not occur, or unwanted events can suddenly occur. Second, exposure takes place between therapy sessions, and thus therapist feedback is retrospective and based on patient reports, which could be inaccurate because of biases[14]. Finally, many patients are reluctant or unable to undergo exposure because of strong paranoid fears or negative symptoms. These limitations could be overcome through virtual reality. The virtual social world is a controlled environment and exercises are done with the guidance of a therapist. Virtual reality is effective and safe for treating anxiety[188]. It is safe to use in people with psychotic disorders[137], and studies suggest promising results for several virtual reality interventions, including for social skills training, auditory hallucinations, and paranoid ideation[12,189]. These findings suggest that virtual-reality-based CBT (VR-CBT) could be an effective, affordable, acceptable, and accessible form of treatment for patients with paranoid ideation and social withdrawal.

We did a randomized controlled trial to establish the effectiveness of VR-CBT, compared with treatment as usual, in improving the quantity and quality of social participation in patients with psychotic disorders who experience paranoid ideation and social avoidance. The primary hypothesis was that VR-CBT would lead to more time spent with other people, and a decrease in momentary paranoia, perceived social threat, and anxiety during real-life social activities. Our secondary hypotheses were that safety behaviors and paranoid ideation would be reduced by VR-CBT, that levels of social anxiety, depression, stigma, cognitive biases, and cognitive limitations would decline, and that social functioning, quality of life, and schematic beliefs would improve. Furthermore, we hypothesized that changes in safety behavior and cognition (biases and mental schemas) would mediate the reduction in paranoia. Cost-effectiveness analyses will be reported in a separate paper.

Methods

Study design and participants

We did a single-blind randomized controlled trial of VR-CBT plus treatment as usual versus treatment as usual only in outpatients at seven Dutch mental health centers. Details of the study protocol have been published[114]. Inclusion criteria were a DSM-IV diagnosis of a psychotic disorder based on the Mini-International Neuropsychiatric Interview[190], the Schedules for Clinical Assessment in Neuropsychiatry[59], or the Comprehensive Assessment of Symptoms and History[60] (varied by center); avoidance of either shops, streets, public transport, or bars or restaurants; paranoid ideation in the past month (defined as a score greater than 40 on the Green et al Paranoid Thoughts Scale[63]); and age 18–65 years. Exclusion criteria were an IQ of 70 or lower (established by a valid instrument such as the Wechsler Adult Intelligence Scale or the Wechsler Intelligence Scale for Children); insufficient mastery of the Dutch language; and history of epilepsy. The protocol was approved by the medical ethical committee of VU University Medical Center Amsterdam (METC number NL37356.058.12). Patients were informed about the study by their treating psychiatrist, psychologist, or psychiatric nurse. If a patient was eligible and willing to participate, written informed consent was obtained.

Randomization and masking

After a baseline assessment, patients were randomly assigned. Research assistants blinded to treatment allocation did the post-treatment and follow-up assessments. Assessors were instructed to stop the assessment in case of unblinding, and the assessment was repeated by another research assistant. (An assessor had to be replaced on three occasions.) Block randomization was used to allocate patients (1:1) to the VR-CBT or control group. Each block had six assignments per condition. If a center had more patients, a second randomized block was allocated. Blocks were made with the scientific randomization program Research Randomizer by the independent randomization bureau of Parnassia, which also allocated patients to groups.

Procedures

The two groups were compared at baseline, after treatment (3 months after baseline), and at follow-up (6 months after baseline). Participants who dropped out of treatment were asked to complete the post-treatment and follow-up assessments. Instructions were given to psychiatrists not to change patients' medication during the study. When patients reported medication changes, these changes were checked with their clinician. No additional psychological treatments for paranoid ideation or social participation were allowed. Participants in the control group were offered VR-CBT after follow-up. Four virtual social environments (a street, bus, café, and supermarket) were created with Vizard software (appendix). Within the environment, participants could move

by operating a Logitech F310 Gamepad. They used a Sony HMZ-T1/T2/T3 Head Mounted Display with a high-definition resolution of 1280×720 per eye, with 51·6 diagonal field of view, and a 3DOF tracker for head rotation. Therapists could vary the number of human avatars (0–40), the characteristics of the avatars (including sex and ethnicity), and the avatars' responses to the patient (neutral or hostile, eye contact) to match the paranoid fears of the patient. Therapists could also make the avatars say pre-recorded sentences. Because these stimuli were directly controlled by the therapist, personalized treatment exercises were created for each patient.

VR-CBT consisted of 16 sessions over 8–12 weeks. Sessions lasted 1 h, 40 min of which comprised virtual-reality exercises. The remaining 20 min were used to plan and reflect on exercises. An individualized case formulation guided exposure to idiosyncratic social environmental cues that elicited fear, paranoid thoughts, and safety behaviors. Patients and therapists communicated during virtual-reality sessions to explore and challenge suspicious thoughts during social situations, drop safety behaviors during social situations (such as avoiding eye contact with, keeping distance from, and refraining from communication with avatars), and test harm expectancies. No homework exercises were given between sessions to test the effects of the in-virtuo exposure without the effects of structured in-vivo exposure. VR-CBT therapists were psychologists with at least basic CBT training. They received 2 days' training in VR-CBT. The VR-CBT manual described a structured treatment plan for all 16 sessions. Therapists were supervised in a group for 4 h every month. All therapy sessions were recorded on audiotapes. Experienced CBT psychologists anonymously rated a random selection of sessions (two per therapist) for treatment fidelity with the Cognitive Therapy Rating Scale[191]. Patients in the waiting list control group received treatment as usual—antipsychotic medication, regular contact with a psychiatrist to control symptoms, and regular contact with a psychiatric nurse to improve self-care, daytime activities, and social and community functioning.

Outcomes

The primary outcome was social participation—a multidimensional construct with a behavioral, objective dimension and a subjective, experiential dimension. We operationalized objective social participation as the amount of time spent with others and subjective social participation as momentary paranoia, perceived social threat, and momentary anxiety in company.

The experience sampling method (ESM)—a structured diary method in which individuals are asked in daily life to report their momentary thoughts, feelings, symptoms, social contexts, and appraisal of social contexts—was used to assess momentary outcomes. ESM has been used by patients with psychotic disorder, with or without symptoms[53]. The method used in this study, PsyMate, has high ecological validity[192]. All participants

carried a PsyMate electronic device for assessments, which beeped at quasi-random moments ten times a day during 6 days. At each beep, the device collected self-assessments on a seven-point Likert scale, ranging from 1 ("not at all") to 7 ("very"). Reports had to be completed within 15 min of the beep. To be included in the analysis, participants had to complete diary entries for at least one-third of the beeps (i.e., a minimum of 20 measurements). For ESM, items from previous studies were used. Principal component analyses have been done previously for ESM affect items, and identified the following factors: negative affect, positive affect, momentary paranoia[193], and perceived social threat[53]. A principal component analysis with oblique rotation and Kaiser normalization for the person-centered data from our study identified these four factors according to the Kaiser criterion (eigenvalue > 1). We used the momentary paranoia and perceived social threat subscales. The principal component analysis confirmed the perceived social threat factor for all four items (factor loadings ranging from 0.57 to 0.80) and partly confirmed momentary paranoia for three items (factor loadings ranging from 0.52 to 0.83). The three-item momentary paranoia subscale was used. Time spent with others was measured by the proportion of beeps that participants reported to be in company of other people (not mental health professionals). Momentary paranoia was calculated as the mean score of the three items: "I feel that others might hurt me", "I feel that others dislike me", and "I feel suspicious". Perceived social threat was calculated as the mean score on the items "I like this company [reversed score]", "In this company, I feel accepted [reversed score]", "I would rather be alone", and "In this company, I feel threatened". Scores on the item "I feel anxious" when in the presence of other people were used to establish momentary anxiety.

Secondary outcomes for symptom measures were the Safety Behaviour Questionnaire-Persecutory Delusions[194], the Green et al Paranoid Thoughts Scale[63], the Social Interaction Anxiety Scale[64], and the Beck Depression Inventory[177]. Functional outcomes were rated with the Social and Occupational Functioning Assessment Scale[101] and the Manchester Short Assessment of Quality of Life[195]. Stigma was assessed with the Internalized Stigma of Mental Illness questionnaire[196]. To examine putative working mechanisms of the therapy, cognitive constructs were assessed with the Brief Core Schema Scales[197] and the self-reported Davos Assessment of Cognitive Biases Scale[87]. Medication adherence was measured with the Brief Adherence Rating Scale[198]. After the fourth and eighth sessions, presence in virtual reality was assessed with the Igroup Presence Questionnaire[199], and cybersickness symptoms with the Simulator Sickness Questionnaire[141].

Statistical analyses

Because, to our knowledge, VR-CBT has never been tested before and ESM had not previously been used as a primary outcome in intervention studies, we conservatively estimated sample size by assuming a moderate effect size of 0.5 with a power of 0.8, an α of 0.05 and a two-sided independent t test. The estimated sample size was 64 for

each group. We postulated an attrition rate of 20%, and thus set 160 as the total sample size. For primary outcomes, we applied the Bonferroni correction for four tests, with a significance level of 0.0125. For all other outcomes, the significance level was .05. Group characteristics were compared at baseline with t tests, non-parametric Mann-Whitney U tests, or χ^2 tests. All data had a hierarchical structure, with repeated measurements (level 1) nested within individuals (level 2). Multilevel analyses were done to take into account that intra-individual observations are more similar than inter-individual observations. Logistic multi-level regression analyses were done for objective social participation; multilevel regression analyses were done for all other outcomes. All models included a random intercept for participant. We used the maximum-likelihood method and the covariance structure identity for estimation. All data were analyzed by intention to treat. The treatment effect was established with the group by time interaction for the post-treatment and follow-up assessments separately. Post-treatment and follow-up data were each compared to baseline. In all analyses age, sex, ethnicity, and education were included as covariates. If baseline differences between groups were noted, this variable was included as a covariate in all analyses. We calculated effect sizes for group by time interaction effects with the z test statistics to determine r[200]. To facilitate interpretation, we transformed r into Cohen's d^{pp} (the superscript shows that the effect size was based on pre–post measures)[201].

Two parallel multiple mediation analyses were done to examine the mediating effects of VR-CBT on paranoid ideation at the post-treatment assessment. The analyses had different outcome measures—paranoid ideation (Green et al Paranoid Thoughts Scale total score) and momentary paranoia (ESM; appendix). Selection of potential mediators was based on the results of our multilevel analysis. We used a significance level of 0.10 for the post-treatment treatment effect variables as the cutoff for inclusion in the mediation analysis. Analyses were done with the PROCESS macro[202], which uses linear regression to estimate indirect effects according to the methods recommended by Hayes and Rockwood for clinical studies[203]. This method is based on a modern framework, and, by contrast with the causal and steps approach, in which a series of criteria are required to establish mediation[204], it focuses solely on quantification of indirect effects. Hayes and Rockwood also emphasize the value of mediation analysis for research if only two measurement moments are used. Post-treatment scores were added as mediators, and baseline scores for the outcome variables and mediators were added to the models as covariates. Least-square path analysis was used and the bootstrap confidence interval (5,000 permutations) was applied to estimate indirect effects. We used Stata (version 13.1) and SPSS (version 24.0.0.0) for all analyses. Because of an oversight, prospective trial registration was overlooked, but the trial was registered retrospectively with ISRCTN, number 12929657. Details of our initial ethics approval and protocol are in the appendix.

Role of the funding source
The study funders had no role in the study design; data collection, analysis, or interpretation; or writing of the Article. RMCAP-K, CNWG, WV, PAEGD, and MvdG had full access to all study data, and RMCAP-K, the corresponding author, had final responsibility for the decision to submit for publication.

Results

Between April 1, 2014, and Dec 31, 2015, 116 patients with a psychotic disorder were randomly assigned (figure 6.1). Patients who were included in the study did not differ significantly in terms of frequency and severity of paranoid ideation from those who chose not to participate (we did separate analyses for patients who were eligible but did not consent to be contacted about study participation, those who had no wish, need, or time for treatment, those who were unable to travel to the treatment location, and those who gave permission for contact but did not respond; data not shown).

Sociodemographic characteristics were well balanced between groups (table 6.1). Participants who dropped out from VR-CBT did not differ from participants who completed VR-CBT in baseline paranoid ideation or safety behaviors (data not shown). We noted

Table 6.1. Characteristics of the study sample at baseline

	VR-CBT N = 58	WL control N = 58
Male	40 (69%)	42 (72%)
Age in years	36.5 (10)	39.5 (10)
Non-Dutch origin	15 (26%)	25 (43%)
Education		
No/primary	16 (28%)	16 (28%)
Vocational	18 (31%)	24 (41%)
Secondary	9 (16%)	9 (16%)
Higher	15 (26%)	9 (16%)
DSM-IV diagnosis		
Schizophrenia	46 (79%)	49 (85%)
Schizoaffective disorder	1 (2%)	5 (9%)
Delusional disorder	1 (2%)	0 (0%)
Psychotic disorder NOS	10 (17%)	4 (7%)
Duration of illness in years	13.3 (10.6)	14.9 (9.5)
Medication use		
Antipsychotics	54 (93%)	57 (98%)
Olanzapine equivalent of prescribed antipsychotic medication (mg/day)	10.5 (6.8)	11.0 (8.3)
Antidepressants	15 (26%)	17 (29%)

Note. Data are n (%) or mean (SD). VR-CBT = virtual reality based cognitive behavioral therapy. NOS = Not Otherwise Specified.

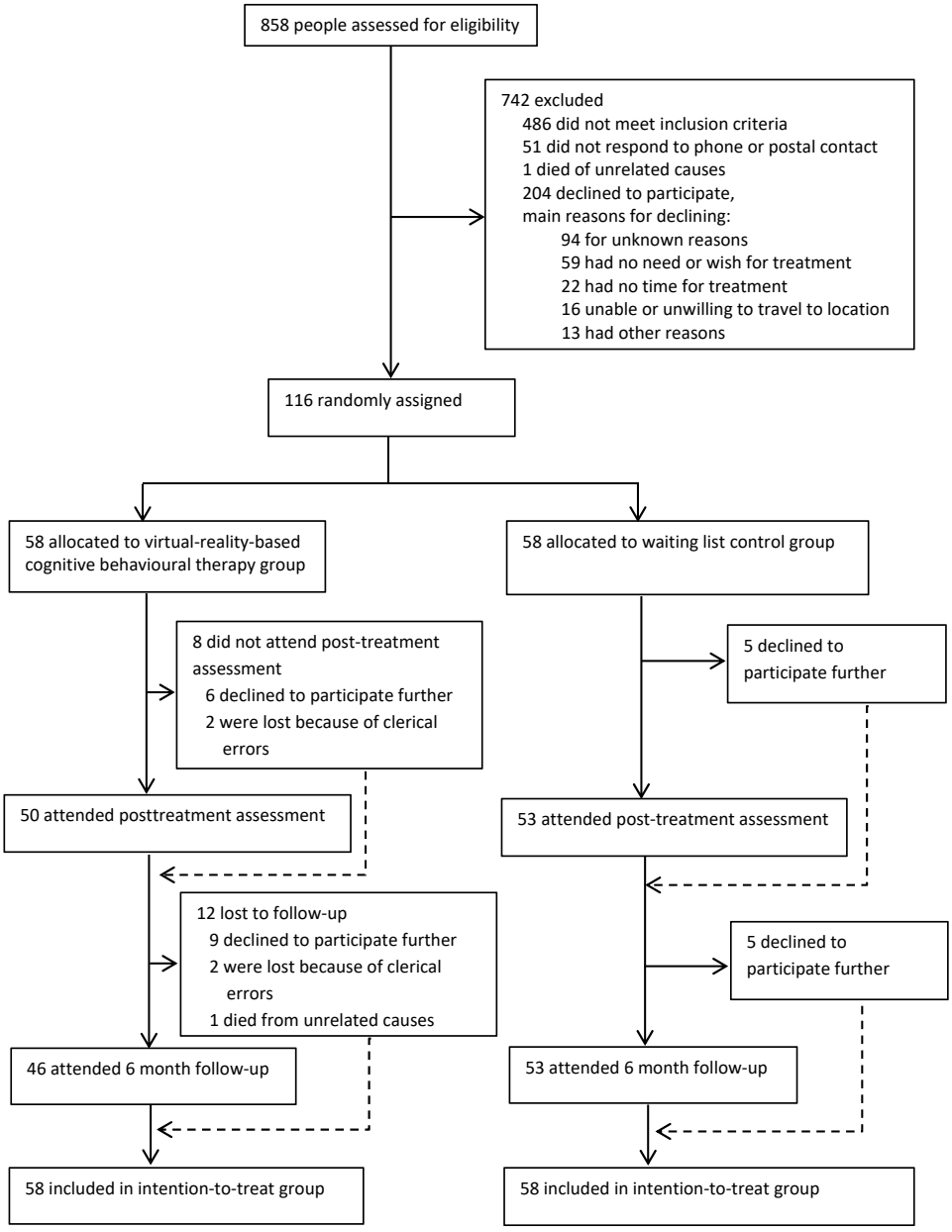

Figure 6.1. Trial profile.

no differences in baseline paranoid ideation or safety behavior between participants who refrained from follow-up measurements and those who completed all measurements (data not shown). Cybersickness was recorded (appendix), but only one participant dropped out because of nausea, rendering further statistical investigation irrelevant. No adverse events relating to either VR-CBT or the assessments were reported.

11 patients (19%) in the VR-CBT group dropped out of therapy (including four who never started treatment). Seven patients discontinued treatment: one was too afraid (completed one session), one had no time (one session), one was not willing to travel to therapy location (two sessions), one had nausea (two sessions), one was unable to attend sessions sober (three sessions), and two found the head-mounted display too uncomfortable to tolerate (five and six sessions, respectively). Participants felt sufficiently present in the virtual environments on all three subscales of the Igroup Presence Questionnaire (range 0–6): spatial presence (mean 3.79), involvement (mean 3.16), and realness (mean 2.96). 28 sessions were rated for treatment fidelity. Therapists had "good" to "very good" adherence to the protocol and CBT quality (mean 4.5 [range 2.4–5.9]).

The VR-CBT group reported 17 changes of anti-psychotics: ten doses were lowered, three doses were raised, and four patients changed medication. 18 changes were reported in the control group: 11 doses were lowered, six doses were raised, and one person changed medication. No significant differences were noted between patients who had any medication changes and those who had no changes at baseline, at 3 months after treatment, or at follow-up (data not shown).

At baseline, no significant differences were noted between the VR-CBT and control groups, except in use of safety behaviors (table 6.2), which was significantly lower in the control group (24.1) than in the VR-CBT group (28.8; z = -2·09; P = .036). Baseline level of safety behaviors was thus included as a covariate in analyses. All participants completed ESM measurements at baseline (mean number of completed self-assessments 46.1 [SD 13.3]), 96 participants completed the post- treatment assessment sufficiently (43.1 [10.1]), and 87 participants completed the follow-up (43.2 [11.1]).

For amount of time spent with others, the treatment effect at the post-treatment visit compared with baseline was not significant (d^{PP} 0.25; P = .178), but the treatment effect at follow-up compared with baseline was (d^{PP} 0.50; P = .0090; table 6.3). Time spent with others decreased by 2.4% in the control group between baseline and the follow-up assessment, whereas the amount of time marginally increased by 0.3% in the VR-CBT group.

Between baseline and the post-treatment assessment, a large reduction was noted in momentary paranoia (-0.350) in the VR-CBT group, whereas a slight increase was noted in the control group (0.162; d^{PP} -1.49; P < .0001; table 6.3). A significantly larger decrease in momentary anxiety was noted in the VR-CBT group than in the control (d^{PP} 0.75; P = .0002; table 6.3). The effect sizes for momentary paranoia and anxiety remained significant at follow-up. When the mean of the original four-item subscale was used (instead of the three-item subscale), the pattern of results for momentary paranoia was identical (data not shown). No significant interaction effects were noted for perceived social threat at the post-treatment (d^{PP} -0.33) or follow-up (d^{PP} 0.36) assessments (table 6.3).

Table 6.2. Means and standard deviations of outcomes measures over time

	VR-CBT			WL control		
	Baseline	Posttreatment	Follow-up	Baseline	Posttreatment	Follow-up
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Primary outcomes						
Time spent with others (ESM)	0.416 (0.26)	0.404 (0.24)	0.419 (0.24)	0.364 (0.27)	0.323 (0.28)	0.340 (0.30)
Momentary paranoia (ESM)	3.064 (1.39)	2.714 (1.38)	2.719 (1.37)	3.140 (1.43)	3.302 (1.60)	3.354 (1.56)
Perceived social threat (ESM)	2.703 (0.86)	2.805 (1.01)	2.728 (1.04)	2.816 (0.91)	2.837 (0.98)	2.752 (0.99)
Momentary anxiety (ESM)	2.986 (1.12)	2.586 (1.14)	2.645 (1.21)	3.259 (1.50)	3.221 (1.56)	3.218 (1.49)
Secondary outcomes						
Ideas of persecution (GPTS)	41.2 (18.9)	33.4 (17.1)	31.4 (17.9)	36.2 (16.3)	38.2 (17.9)	38.4 (18.7)
Ideas of social reference (GPTS)	43.6 (15.9)	35.4 (15.5)	34.0 (16.1)	40.4 (15.7)	38.7 (14.9)	39.1 (15.4)
Safety behaviours (SBQ-PD)[a]	28.8 (14.2)[a]	21.1(16.0)	20.2 (16.2)	24.1 (15.0)[a]	23.8 (16.5)	22.5 (13.5)
Social interaction anxiety (SIAS)	43.8 (13.1)	36.8 (13.1)	36.2 (13.0)	43.1 (14.9)	39.2 (15.7)	40.3 (15.1)
Depression inventory (BDI-II)	17.2 (9.5)	16.0 (10.4)	13.3 (10.1)	17.6 (9.7)	15.0 (10.0)	15.8 (9.9)
Quality of life (MANSA)	4.3 (0.9)	4.3 (1.0)	4.4 (1.0)	4.2 (0.9)	4.3 (0.8)	4.3 (0.8)
Social functioning (SOFAS)	49.6 (8.0)	50.1 (8.7)	51.4 (10.7)	49.6 (8.3)	49.5 (8.6)	47.6 (8.6)
Stigma (ISMI)	2.4 (0.3)	2.3 (0.4)	2.2 (0.4)	2.4 (0.4)	2.4 (0.5)	2.4 (0.4)

Table 6.2 continues on next page.

Table 6.2. ***Continued***

	VR-CBT			WL control		
	Baseline	Posttreatment	Follow-up	Baseline	Posttreatment	Follow-up
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Jumping to conclusions (DACOBS)	26.8 (5.4)	25.4 (5.6)	25.4 (5.3)	25.0 (5.1)	25.2 (5.3)	24.8 (5.9)
Belief inflexibility (DACOBS)	22.6 (5.6)	23.1 (6.6)	22.2 (6.2)	22.0 (5.2)	22.0 (5.3)	21.5 (4.7)
Attention for threat (DACOBS)	29.6 (6.1)	27.7 (7.2)	27.6 (7.2)	28.0 (6.4)	28.5 6.2)	27.9 (6.1)
External attribution (DACOBS)	24.8 (6.8)	24.3 (6.7)	22.8 (6.3)	24.3 (7.0)	23.8 (6.4)	24.1 (6.7)
Social cognitive problems (DACOBS)	29.7 (6.1)	27.4 (7.1)	26.6 (6.8)	27.5 (6.0)	27.5 (6.2)	27.6 (6.3)
Subjective cognitive problems (DACOBS)	26.1 (5.5)	25.9 (6.3)	25.2 (6.4)	26.2 (6.7)	26.5 (6.1)	25.0 (5.6)
Safety behaviour (DACOBS)	22.8 (6.5)	20.5 (6.5)	20.3 (7.1)	20.2 (7.4)	20.0 (7.8)	20.4 (7.1)
Negative self core schema (BCSS)	5.8 (4.7)	4.8 (4.6)	4.6 (4.5)	5.6 (4.5)	4.8 (4.3)	5.1 (4.0)
Negative others core schema (BCSS)	6.6 (7.2)	5.1 (6.5)	5.0 (6.5)	5.6 (6.2)	5.3 (5.9)	5.8 (6.5)
Positive self core schema (BCSS)	8.3 (5.3)	8.4 (6.1)	8.9 (6.0)	7.0 (4.2)	8.1 (5.1)	7.1 (4.5)
Positive others core schema (BCSS)	7.9 (5.3)	8.1 (6.1)	9.3 (6.5)	6.2 (5.2)	6.9 (5.9)	6.5 (4.6)

Note. M = mean. SD = standard deviation. ESM = Experience Sampling Method. GPTS = Green et al. Paranoid Thoughts Scale. SBQ-PD = Safety Behaviour Questionnaire - Persecutory Delusions. SIAS = Social Interaction Anxiety Scale. BDI-II = The Beck Depression Inventory. MANSA = The Manchester Short Assessment of Quality of Life. SOFAS = The Social and Occupational Functioning Assessment Scale. ISMI = Internalized Stigma of Mental Illness. DACOBS = The Davos Assessment of Cognitive Biases Scale. BCSS = Brief Core Schema Scales.

Table 6.3. Between-group tests and effect sizes (Cohen's d) at posttreatment and at six-months follow-up

	Posttreatment						Six-month follow-up					
	b	SE	z	P	[95% CI]	Effect size d	b	SE	z	P	[95% CI]	Effect size d
Primary outcomes												
Time spent with others (ESM)	0.140	0.10	1.35	0.178	-0.064 to 0.344	0.25	0.288	0.11	**2.61**	**0.0090**	0.072 to 0.502	0.50
Momentary paranoia (ESM)	-0.331	0.05	**-6.44**	**< 0.0001**	-0.432 to -0.230	-1.49	-0.287	0.05	**-5.69**	**< 0.0001**	-0.385 to -0.188	-1.24
Perceived social threat (ESM)	-0.099	0.06	-1.73	0.084	-0.211 to 0.013	-0.33	0.107	0.06	1.89	0.059	-0.004 to 0.219	0.36
Momentary anxiety (ESM)	-0.288	0.08	**-3.78**	**0.0002**	-0.438 to -0.139	-0.75	-0.207	0.08	**-2.70**	**0.0070**	-0.358 to -0.057	-0.52
Secondary outcomes												
Ideas of persecution (GPTS)	-8.59	2.42	-3.55	**0.0004**	-13.32 to -3.85	-0.70	-9.68	2.47	-3.91	**0.0001**	-14.52 to -4.83	-0.78
Ideas of social reference (GPTS)	-5.53	2.41	-2.29	**0.022**	-10.26 to -0.80	-0.44	-6.25	2.20	-2.84	**0.0045**	-10.56 to -1.94	-0.55
Safety behaviours (SBQ-PD)	-6.13	2.41	-2.55	**0.011**	-10.85 to -1.42	-0.49	-5.19	2.34	-2.21	**0.027**	-9.79 to -0.60	-0.42
Social interaction anxiety (SIAS)	-2.71	2.15	-1.26	0.209	-6.93 to 1.51	-0.24	-3.38	1.94	-1.74	0.082	-7.18 to 0.43	-0.33
Depression inventory (BDI)	1.32	1.39	0.95	0.341	-1.40 to 4.05	0.18	-0.85	1.54	-0.55	0.582	-3.87 to 2.18	-0.10
Quality of life (MANSA)	-0.01	0.11	-0.07	0.942	-0.22 to 0.22	-0.01	-0.00	0.11	-0.04	0.966	-0.23 to 0.22	-0.01
Social functioning (SOFAS)	1.22	1.37	0.89	0.372	-1.46 to 3.90	0.17	3.73	1.66	2.25	**0.024**	0.48 to 6.98	0.43
Stigma (ISMI)	-0.04	0.06	-0.61	0.540	-0.16 to 0.08	-0.11	-0.13	0.06	-2.32	**0.020**	-0.25 to -0.02	-0.44

Table 6.3 continues on next page.

Table 6.3. ***Continued***

	Posttreatment						Six-month follow-up					
	b	SE	z	P	[95% CI]	Effect size d	b	SE	z	P	[95% CI]	Effect size d
Jumping to conclusions (DACOBS)	-1.51	0.84	-1.80	0.072	-3.16 to 0.13	-0.34	-0.93	0.88	-1.05	0.294	-2.66 to 0.80	-0.20
Belief inflexibility (DACOBS)	0.42	0.92	0.46	0.646	-1.38 to 2.22	0.09	0.34	0.83	0.42	0.677	-1.28 to 1.97	0.08
Attention for threat (DACOBS)	-2.11	0.95	**-2.23**	**0.026**	-3.97 to -0.26	-0.42	-1.11	0.95	-1.18	0.239	-2.97 to 0.74	-0.22
External attribution (DACOBS)	0.25	0.99	0.25	0.803	-1.70 to 2.20	0.05	-0.73	1.02	-0.71	0.480	-2.74 to 1.29	-0.13
Social cognitive problems (DACOBS)	-1.84	0.90	**-2.04**	**0.041**	-3.60 to -0.08	-0.39	-2.35	1.01	**-2.32**	**0.021**	-4.33 to -0.36	-0.44
Subjective cognitive problems (DACOBS)	-0.45	0.88	-0.51	0.607	-2.17 to 1.27	-0.09	-0.33	1.06	-0.32	0.749	-2.42 to 1.74	-0.06
Safety behaviour (DACOBS)	-1.42	0.95	-1.49	0.136	-3.29 to 0.45	-0.28	-1.58	1.00	-1.59	0.113	-3.53 to 0.37	-0.30
Negative self core schema (BCSS)	-0.25	0.66	-0.37	0.710	-1.54 to 1.05	-0.07	-0.13	0.65	-0.19	0.845	-1.40 to 1.15	-0.04
Negative others core schema (BCSS)	-1.09	0.79	-1.39	0.165	-2.63 to 0.45	-0.26	-0.88	0.76	-1.15	0.248	-2.38 to 0.61	-0.21
Positive self core schema (BCSS)	-0.91	0.80	-1.13	0.257	-2.48 to 0.66	-0.21	0.20	0.69	0.29	0.774	-1.16 to 1.55	0.05
Positive others core schema (BCSS)	-0.73	0.80	-0.92	0.360	-2.31 to 0.84	-0.17	0.62	0.84	0.74	0.459	-1.03 to 2.28	-0.14

Note. Treatment effects are shown (the interaction effect of time and treatment condition). Separate multilevel regression models were estimated for baseline-posttreatment and baseline-follow-up data. SE = standard error. CI = confidence interval. ESM = Experience Sampling Method. GPTS = Green et al. Paranoid Thoughts Scale. SBQ-PD = Safety Behaviour Questionnaire - Persecutory Delusions. SIAS = Social Interaction Anxiety Scale. BDI-II = The Beck Depression Inventory. MANSA = The Manchester Short Assessment of Quality of Life. SOFAS = The Social and Occupational Functioning Assessment Scale. ISMI = Internalized Stigma of Mental Illness. DACOBS = The Davos Assessment of Cognitive Biases Scale. BCSS = Brief Core Schema Scales. Age, ethnicity, education, sex and baseline safety behaviour were included as covariates in all analysis.

Compared with the control group, use of safety behaviors decreased significantly in the VR-CBT group at both the post-treatment and follow-up assessment (table 6.3). The largest reduction at the post-treatment visit was for the in-situ safety behaviors subscale ($b^{interaction}$ – 3.7 [95% CI -6.2 to -1.2]; z -2.93, P = .0033).

Treatment effects on paranoid ideation were significant: at the post-treatment and follow-up assessments, levels of ideas of persecution and social reference were lower in the VR-CBT group than in the control group (table 6.3). Depression and anxiety were not significantly lower in the intervention than in the control group (table 6.3). The VR-CBT group had improvements in self-stigmatization and social functioning at follow-up whereas the control group did not (table 6.3). Quality of life at the post-treatment or follow-up assessments did not differ significantly between groups (table 6.3).

Significant interaction effects were noted for attention for threat and social cognitive problems at the post-treatment assessment (table 6.3). No significant treatment effects were found for positive and negative beliefs of self or others (table 6.3).

Mediation analysis showed that part of the treatment effect on paranoid ideation (measured by the Green et al Paranoid Thoughts Scale) at the post-treatment assessment was mediated by change in safety behavior (percentage mediated 33.7%) and change in social cognitive problems (percentage mediated 19.2%; table 6.3). Individuals who received VR-CBT used less safety behavior and reported fewer social cognition problems than did those in the control group, and in turn experienced less paranoid ideation. Jumping to conclusions and attention for threat did not mediate the effect of treatment on paranoid ideation (table 6.4). The direct effect of the treatment on paranoid ideation was no longer significant after inclusion of the mediators in the model (P = .060). The indirect effect of safety behavior was not significantly larger than the indirect effect of social cognition problems (bootstrap CI of the contrast -3.4 to 7.5). None of the included mediators significantly mediated the effect of VR-CBT on momentary paranoia as measured with ESM (table 6.4). The total effect (independent of mediators) and direct effect (including the mediators) of treatment were both significant for momentary paranoia (table 6.4).

Discussion

To our knowledge, ours is the first randomized controlled trial of VR-CBT to treat paranoid ideation and social avoidance in patients with psychotic disorders. Although the amount of time spent with others did not increase after VR-CBT compared with the control, VR-CBT resulted in large reductions in momentary paranoia and anxiety during social interactions, not only at the post-treatment assessment, but also at the 6-month follow-up assessment. Significant improvements were also noted for ideas of

Table 6.4. Results mediation analyses*

		Paranoid ideation (GPTS)			Momentary paranoia (ESM)		
		N = 101			N = 95		
		Effect	P	95% boot CI	Effect	P	95% boot CI
Total effect	c	13.72	**0.0024**		0.38	**0.012**	
Direct effect	c'	6.83	0.060		0.28	**0.042**	
Indirect effect safety behaviour	ab1	4.62		**0.62 to 10.21**	0.02		-0.01 to 0.26
Indirect effect attention for threat	ab2	-0.35		-3.86 to 1.71	0.06		-0.01 to 0.23
Indirect effect social cognitive problems	ab3	2.63		**0.05 to 8.01**	0.05		-0.03 to 0.25
Indirect effect jumping to conclusions	ab4	-0.01		-1.49 to 1.49	-0.03		-0.17 to 0.01

Note. Boot CI = bootstrap confidence interval. ESM = Experience Sampling Method. GPTS = Green et al. Paranoid Thoughts Scale.

* Mediation analysis was performed by the method described by Hayes and Rockwood[203]. Baseline and posttreatment values were used, baseline values of outcome and mediator variables were added as covariates to the model.

persecution, ideas of social reference, and use of safety behavior. The therapeutic effect of VR-CBT for paranoid ideation was mediated by improvements in safety behaviors and social cognition, but mediation effects were not noted for momentary paranoia. Our findings suggest that VR-CBT does not immediately lead to spending more time with others, but helps patients to learn how to drop safety behaviors and to have social interactions more positively, with less anxiety and paranoia after therapy. In turn, these positive experiences seem to lead to fewer paranoid thoughts and fewer ideas of social reference in general. This interpretation was supported by the results of the mediation analysis, which showed that reductions in safety behavior accounted for 34% of the change in paranoid ideation, and improvements in social cognition for 19%.

How do these mechanisms contribute to reductions in paranoid ideation? Safety behaviors interfere with the development of new associations and prevent gathering of social information. For example, during the first sessions, many participants looked at avatars from the neck down only, avoiding eye contact. When such safety behavior is dropped, the patient receives more social information. Improvements in social cognition can result in more adequate interpretations of that information, thereby reducing the chance of incorrect paranoid appraisals. Safety behavior was targeted explicitly during sessions, because people practiced within virtual recreations of situations that they would usually avoid. Cognition was actively challenged and discussed during virtual reality exposures, although in a less structured fashion than safety behavior, which could explain the absences of findings for several cognitive biases.

No mediating effects were identified for momentary paranoia as measured by ESM. Although this finding seems contradictory to the results for paranoid ideation on the Green et al Paranoid Thoughts Scale, it could be explained by the nature of the scales. The Green et al Paranoid Thoughts Scale assesses paranoia with 32 items, whereas momentary paranoia is composed of three items. Thus, variation in ESM scores tends to be lower, and the ESM scale might be less sensitive to changes. Additionally, retrospectively measured paranoid ideation could capture different constructs from those captured by measurement of momentary state paranoia. ESM is ecologically valid, but also seems to be complementary to retrospective measures rather than a measurement of the same constructs[205].

Overall, expansion of social activities and improvement of social functioning seem to require more time and are mainly accomplished in the period after therapy. Patients in symptomatic remission do not immediately spend more time with others[206]. When patients increasingly feel more comfortable in social situations and learn that other people are less threatening than anticipated, they might try and succeed to make and maintain social contacts and find hobbies and jobs. At the follow-up assessment in our study, a positive effect of VR-CBT was noted for stigma and social and occupational functioning. Furthermore, resolution of symptoms might not automatically improve social functioning—negative symptoms and deficient social skills could get in the way. Additional training might be needed.

Our results are in line with a virtual reality experimental study[115] for treatment of ideas of persecution, in which significant reductions in delusional conviction and real-world distress were noted after one session. Similar to virtual reality interventions for social skills and job interview training for people with schizophrenia, our intervention was generalizable to everyday life[12]. Although many virtual reality studies have a high frequency of dropouts due to cybersickness[6], in our study only one participant had cybersickness to the extent that he quit treatment. SSQ data can be found in supplementary table S6.1. Cybersickness might become less of a problem as a result of improvements in technology. Perception of social threat, as measured by ESM, was not significantly affected by VR-CBT. Collip and colleagues[53] noted that perceived social threat was more often reported in the company of less familiar people than in the presence of familiar people. However, the term social threat could be misleading, because the items on the ESM could also express the wish to enjoy company versus a preference for being alone. This scale thus needs further validation.

A strength of our study is the use of ESM to assess treatment effects in the flow of daily life. Another strength is the pragmatic effectiveness design of the study. The study was done in seven mental health centers, and treatment was delivered within standard services by regularly employed therapists. Therapists' experience with exposure therapy and CBT varied. Our results suggest the effectiveness of VR-CBT in real-world conditions in a sample of patients who are representative of standard clinical practice.

Our study also had several limitations. First, we did not use an active control group, such as CBT with exposure in vivo. Thus, we cannot rule out a dose-effect of therapeutic contacts. Second, the long-term effects of VR-CBT remain unknown, because follow-up was restricted to 6 months. Third, technological limitations restricted conversational interaction possibilities between participants and avatars. Therefore VR-CBT could not sufficiently address conversational issues. Fourth, a potential limitation of VR-CBT is that patients are not exposed to unexpected surprises that can occur in life. Although this criticism is valid, many patients with psychosis become too frightened in real-life situations, preventing them from dropping safety behaviors or causing them to avoid exposure. To prevent the risk that the presence of the therapist becomes a safety signal, as therapy progresses the therapist should become less prominently present and should guide the patient less. Fifth, some eligible patients did not participate because they were too frightened to travel to the therapy location. Thus, our sample might have been biased, because some of the most paranoid and avoidant patients could not participate. Additionally, little is known about the patients who seemed eligible on the basis of screening but did not consent to be contacted, or about the people who provided consent to be contacted, but did not respond. Further-more, we could not recruit the aimed number of participants within our financial and time limits. The study is thus somewhat underpowered. Finally, the temporal order of the mediation analysis was based on the assumed mechanisms of VR-CBT, but reverse causality cannot be ruled out. That said, we agree with Hayes and Rockwood[203] that mediation analysis, despite limitations, provides useful insights into clinical research findings. Although no final conclusions can be drawn, our findings support the predetermined hypothesis.

In conclusion, in patients with a psychotic disorder, our findings support the hypothesis that VR-CBT strongly reduces paranoid ideation, momentary anxiety, and safety behaviors in real-life social situations. This study shows that targeting safety behavior and social cognitive appraisals in psychotherapy with virtual reality can effectively reduce paranoid thoughts. Future research should compare VR-CBT with standard cognitive behavioral therapy in terms of both treatment effects and cost-effectiveness.

Contributors

RMCAP-K, WV, and MvdG conceived and designed the study. MvdG obtained funding for the trial, then RMCAP-K obtained additional funding. The study was supervised by WV and MvdG. All authors acquired and interpreted data, and provided administrative, technical, or material support. RMCAP-K, CNWG WV, PAEGD, and MvdG did the statistical analysis. RMCAP-K and CNWG drafted the Article, which was critically revised by all authors.

Research in context

Evidence before this study

Paranoid ideation is common in patients with a psychotic disorder. The anxiety resulting from paranoid ideation strongly contributes to social avoidance. Cognitive behavioural therapy is the best-documented effective psychological treatment for this, but effects are small to medium at best. The positive results of using virtual reality in treating anxiety disorders suggest virtual reality might be used to improve treatment for anxiety and avoidance of social situations resulting from paranoid ideation. We searched for the use of virtual reality in treating paranoid ideation. Research showed it is safe to expose patients with a psychotic disorder to immersive virtual environments. It also showed virtual reality can be used to elicit paranoid ideation and anxiety in patients with a psychotic disorder, indicating feasibility of creating virtual environments for treatment.

On 14 september 2017, we searched the entire archive (i.e., using no date or language restrictions) of MedLine for (Virtual Reality) AND (Delus* OR Paranoi* OR Psychosis OR Psychotic OR Schizophren*). Ninety-four peer reviewed papers were identified, and only one was a randomised controlled trial of virtual reality therapy for reducing paranoid ideation. This small (n = 30) experimental study found large reductions in delusional conviction and real-world distress.

Added value of this study

We undertook the first randomised controlled trial to date of virtual reality therapy to improve daily life social functioning and to reduce paranoid ideation in patients with a psychotic disorder. We found that virtual reality based cognitive behavioural therapy strongly reduces paranoid ideation, anxiety and use of safety behaviours in social situations. Results of the mediation analysis support the importance of reducing safety behaviours and modifying social cognition in the treatment of paranoid delusions.

Supplementary material

Supplementary table S6.1. Cybersickness levels after VR-CBT session 4 and session 8

	VR-CBT M (SD)
Session 4	
SSQ total score	57.5 (38.3)
SSQ – Oculomotor subscale	49.9 (31.1)
SSQ – Nausea subscale	42.9 (34.1)
SSQ – Disorientation subscale	59.6 (50.8)
Session 8	
SSQ total score	52.9 (41.9)
SSQ – Oculomotor subscale	45.5 (35.1)
SSQ – Nausea subscale	42.0 (32.3)
SSQ – Disorientation subscale	50.6 (55.0)

Note. Data are mean (SD). VR-CBT = virtual reality based cognitive behavioral therapy. SSQ = Simulator sickness questionnaire.

Chapter 7

Cost-effectiveness of virtual reality cognitive behavioral therapy for psychosis: Health-economic evaluation within a randomized controlled trial

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Abstract

Background: Evidence was found for the effectiveness of virtual reality-based cognitive behavioral therapy (VR-CBT) for treating paranoia in psychosis, but health-economic evaluations are lacking.

Objective: This study aimed to determine the short-term cost-effectiveness of VR-CBT.

Methods: The health-economic evaluation was embedded in a randomized controlled trial evaluating VR-CBT in 116 patients with a psychotic disorder suffering from paranoid ideation. The control group (n = 58) received treatment as usual (TAU) for psychotic disorders in accordance with the clinical guidelines. The experimental group (n = 58) received TAU complemented with add-on VR-CBT to reduce paranoid ideation and social avoidance. Data were collected at baseline and at 3 and 6 months postbaseline. Treatment response was defined as a pre-post improvement of symptoms of at least 20% in social participation measures. Change in quality-adjusted life years (QALYs) was estimated by using Sanderson et al.'s conversion factor to map a change in the standardized mean difference of Green's Paranoid Thoughts Scale score on a corresponding change in utility. The incremental cost-effectiveness ratios were calculated using 5000 bootstraps of seemingly unrelated regression equations of costs and effects. The cost-effectiveness acceptability curves were graphed for the costs per treatment responder gained and per QALY gained.

Results: The average mean incremental costs for a treatment responder on social participation ranged between €8,079 and €19,525, with 90.74%–99.74% showing improvement. The average incremental cost per QALY was €48,868 over the 6 months of follow-up, with 99.98% showing improved QALYs. Sensitivity analyses show costs to be lower when relevant baseline differences were included in the analysis. Average costs per treatment responder now ranged between €6,800 and €16,597, while the average cost per QALY gained was €42,030.

Conclusions: This study demonstrates that offering VR-CBT to patients with paranoid delusions is an economically viable approach toward improving patients' health in a cost-effective manner. Long-term effects need further research.

Introduction

Psychotic disorders impose a large disease burden—morbidity plus mortality—on the population, and in its wake, substantial economic costs occur for society and health care systems. The main drivers of societal costs of schizophrenia are health care costs and productivity losses, but patients and their families also incur substantial costs[207]. Low participation rates of individuals with psychosis in the labor market are an important cause of productivity losses, while the main contributor to health care costs are in-patient psychiatric admissions[208]. All in all, treatment costs of psychotic disorders consume a significant part of health care budgets in European countries[209].

Paranoid ideation is a common delusion in individuals with a psychotic disorder. Even when medicinal treatment is successful, paranoid thoughts and anxiety often remain because of conditioned avoidance and other acquired safety behaviors in social situations[18]. Social avoidance hinders recovery in social participation for patients and keeps unemployment rates as high as 70%–85%[26,210]. A poor social network contributes to stigma and a lack of empowerment, resulting in more depressive symptoms and lower quality of life[211]. A smaller social network size is associated with more severe overall psychiatric and negative symptoms[212]. Virtual reality-based cognitive behavioral therapy (VR-CBT) was found to be an effective treatment for paranoid ideation in individuals with a psychotic disorder[115,213]. The use of virtual reality (VR) treatment in clinical practice is expected to become more widespread as VR technology becomes more readily available[6]. Therefore, information on the cost-effectiveness of this kind of treatment is required. This study was designed to evaluate whether adding VR-CBT to treatment as usual (TAU) would be effective in treating paranoid ideation in a cost-effective way with respect to improving social participation. A trial-based cost-effectiveness analysis (CEA) was conducted using data collected in seven outpatient mental health care services in the Netherlands, comparing add-on VR-CBT with TAU alone. This paper aims to determine the short-term (i.e., 6-month) cost-effectiveness of VR-CBT from a societal perspective.

Methods

Research design

The health-economic evaluation was embedded in a randomized controlled trial evaluating VR-CBT in 116 patients with a psychotic disorder suffering from paranoid ideation[213]. The VR-CBT study was a randomized, controlled, single-blind multicenter trial in two parallel groups, comparing add-on VR-CBT to TAU alone over a period of 6 months[213]. This study was approved by the Vrije Universiteit (VU University) Medical Ethics Committee for mental health service research and was registered retrospectively

at the ISRCTN (International Standard Randomized Controlled Trial Number) registry (ISRCTN12929657). The trial protocol is provided elsewhere[114]. Four virtual social environments—a street, bus, café, and supermarket—were created with Vizard software (WorldViz). Within the environment, participants could move by operating a Logitech F310 Gamepad. They used a Sony HMZ-T1/T2/T3 head-mounted display with a high-definition resolution of 1280 × 720 per eye, a 51.6 diagonal field of view, and a 3DOF (3 degrees of freedom) tracker for head rotation. VR-CBT therapists were psychologists with at least basic cognitive behavioral therapy (CBT) training. They received 2 days of training in VR-CBT. The VR-CBT manual described a structured treatment plan for all 16 sessions. Therapists were supervised in a group for 4 hours every month by two VR-CBT specialists.

Recruitment

Participants were recruited at seven treatment centers in the Netherlands between April 1, 2014, and December 31, 2015. To be included, participants had to meet the following criteria: (1) 18–65 years of age; (2) DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified; (3) suffering from at least mild paranoia, as assessed by Green's Paranoid Thoughts Scale (GPTS) (score of > 40); and (4) self-report of avoiding at least one social situation. Exclusion criteria were as follows: (1) insufficient competency of Dutch language; (2) IQ below 70; and (3) a concurrent diagnosis of epilepsy. Assessments were performed at baseline and at 3 and 6 months postbaseline.

Interventions

All participants continued to receive TAU (i.e., antipsychotic medication, regular contact with a psychiatrist to manage symptoms, and regular contact with a psychiatric nurse). Participants in the experimental condition also received therapist-led VR-CBT. VR-CBT treatment consisted of 16 biweekly sessions of 60 minutes each, using 40 minutes for exposure and behavioral exercises in virtual social environments. The therapist used an individual case formulation to help patients falsify their harm expectancies. No homework exercises were given between VR-CBT sessions. The treatment protocol, in Dutch, is available from the corresponding author.

Outcome measures

0verview

We conducted both a CEA with three measures of improved social participation as outcome and a cost-utility analysis (CUA) with quality-adjusted life years (QALYs) gained as outcome. The outcome measures are described in more detail below.

Social participation

The outcome of interest in the CEA was social participation. Social participation was operationalized in three ways: (1) objective social participation as the amount of time spent with others, (2) subjective social participation as momentary anxiety, and (3) subjective social participation as momentary paranoia. Momentary in this context meant that it was measured in real life during social company. All three outcomes were assessed in real time using the ecological sampling method (ESM). ESM is a structured diary method in which individuals are asked in daily life to report their thoughts, feelings, and symptoms, as well as the appraisal of the present social context. To that end, all participants carried an electronic device (PsyMate) for the ESM assessments. The device beeped at semirandom moments 10 times a day over 6 days. At each beep, the device collected self-assessments on a 7-point Likert scale ranging from 1 (not at all) to 7 (very). A positive treatment response on each of the three outcome measures was defined as an improvement of at least 20% at 6 months follow-up relative to the patient's baseline score.

Quality-adjusted life year

The outcome in the CUA was the QALY derived from the GPTS[63]. The GPTS is an established broad measure of paranoid-delusional functioning that has long been used as an outcome measure. This instrument was chosen to be able to compare results with earlier CUA research on the subject. Mean GPTS scores at each measurement were first converted into the standard mean difference (SMD) by dividing the raw mean change scores by the SD of the GPTS at baseline in the control condition. In a next step, we used Sanderson et al.'s conversion factor[214] of 0.1835 (i.e., the average of 0.209 using a rating scale and 0.158 using time trade-off), such that a change of 1 standard unit (i.e., SMD) on the GPTS is equal to a corresponding change of 0.18 utility. The utility is a quality of life valuation and is needed to compute QALY gains in the VR-CBT condition relative to the TAU condition over the full 6 months between baseline and follow-up.

Resource use and costing

Societal costs were computed by adding (1) the direct medical costs of health care services use including the costs of antipsychotic medication and, in the experimental condition, the additional costs of adjunctive VR-CBT treatment; (2) direct nonmedical costs of travel; and (3) indirect costs stemming from lower productivity. For each participant, cost data over the last 3 months were collected at each of three measurement points. Resource use data, for costing, were collected using the Trimbos Institute and Institute of Medical Technology Assessment Questionnaire for Costs Associated with Psychiatric Illness (TiC-P)[215]. The TiC-P is the most widely used health service interview in the Netherlands. It consists of questions on the number of contacts by type of health care

provider and questions on productivity losses. A health service questionnaire is a valid and reliable method for quantifying costs in trial-based economic evaluations in health care[216]. A cross-validation sample comparing TiC-P self-report to electronic patient files showed all data to be reliable, except for the number of reported sessions with a psychologist (data available upon request from first author). Not all patients had understood that they needed to incorporate the 16 VR-CBT sessions into their TiC-P self-report. This information was, therefore, 100% cross-checked using electronic patient files. The main cost driver was admission to psychiatric hospitals, so the number of days admitted to a psychiatric hospital was also 100% cross-checked against electronic patient files and corrected where needed. Direct medical costs were calculated by multiplying health service units (e.g., sessions, visits, and hospital days) with their standard economic cost price (see supplementary table S7.1). We also added the medication costs, consisting of antipsychotic and antidepressant medication. Corresponding costs were calculated as the cost price per standard daily dose, as reported in the Dutch Pharmaceutical Compass[217], multiplied by the number of prescription days, plus the pharmacist's dispensing costs of €6 per monthly prescription or €12 for a first-time prescription[218].

Virtual Reality Costs for VR therapy hardware, software and training costs were calculated. Total yearly costs for one VR system was €23,995, according to CleVR BV, a company who builds VR sets. Yearly costs for training and supervision of the psychologists was €13,400. Per-patient costs per 16 VR-CBT treatment sessions was €373.95.

Travel Costs Travel costs arose when participants had to make return trips for receiving health care at health services. Travel costs were computed as the average distance to a health service (7 km) multiplied by the costs per km (€0.21)[218].

Productivity Costs Research assistants monitored changes in the participants' work status at baseline and at 3 and 6 months postbaseline using the TiC-P. Productivity losses in paid work were calculated according to the human capital approach[219], reflecting changes in the contractual number of hours worked per week and adjusting these for work-loss days arising from sick leave over the full period of 6 months using gender-specific hourly productivity costs[218]. Costs were originally expressed in Euros for the reference year 2014, but indexed to 2015 using the consumer price index as reported by Statistics Netherlands. In the reference year 2015, 1 Euro in the Netherlands equaled 1.235 US$.

Statistical analysis

Imputation Following the CONSORT (Consolidated Standards of Reporting Trials) and CHEERS (Consolidated Health Economic Evaluation Reporting Standards) guidelines, all our analyses adhered to the intention-to-treat principle. To that end, missing values

were imputed using multiply imputed chained equations (MICE) for nonparametric data with M of 100 bootstraps for each incomplete variable. Baseline variables predictive of effects (i.e., QALYs and treatment response) were used for imputation, such as baseline data of the variable with missing values, treatment condition, ethnicity, education, sex, age, and safety behaviors at baseline. Safety behaviors, such as avoiding eye contact or escaping from social situations, were measured using the Safety Behaviour Questionnaire-Persecutory Delusions (SBQ-PD)[194]. Time spent with others showed a large difference at baseline despite randomization and was added as covariate in the CEA where time spent with others was used as the treatment response outcome of interest. Main Analysis Both the CUA and CEA were conducted from the societal perspective. In each of these analyses, the incremental cost-effectiveness ratios (ICERs) were calculated as the between-group cost difference divided by the between-group effect difference. The ICER is interpreted as the additional costs per additional unit effect (i.e., per additional treatment responder; per QALY gained). Cost and effect differences were obtained from seemingly unrelated regression equations of costs and effects, thus allowing for correlated residuals in the equations. The seemingly unrelated regression equations (SURE) models were bootstrapped 5,000 times. In each bootstrap step, the mean cost differences and the mean outcome differences were computed and these were plotted on the cost-effectiveness plane. Finally, cost-effectiveness acceptability curves (CEACs) were graphed. CEACs inform decision makers about the likelihood that an intervention is deemed cost-effective, given a range of willingness-to-pay ceilings for gaining 1 QALY and gaining 1 treatment responder. All analyses were conducted in Stata, version 13.1 (StataCorp).

Sensitivity analyses

The following sensitivity analyses were carried out. First, a sensitivity analysis was done including safety behavior at baseline as a covariate because despite randomization there was a significant difference at baseline, and it was found to be the main mediator in reducing paranoid ideation213. Second, a sensitivity analysis was done including psychiatric admission costs at baseline as a covariate because there was a large difference between groups at baseline. Third, a sensitivity analysis was done including both safety behavior at baseline and psychiatric admission costs at baseline as covariates in the model.

Results

Overview

After providing informed consent, 116 participants agreed to participate: 58 (50.0%) in the control condition and 58 (50.0%) in the experimental condition (see figure 7.1).

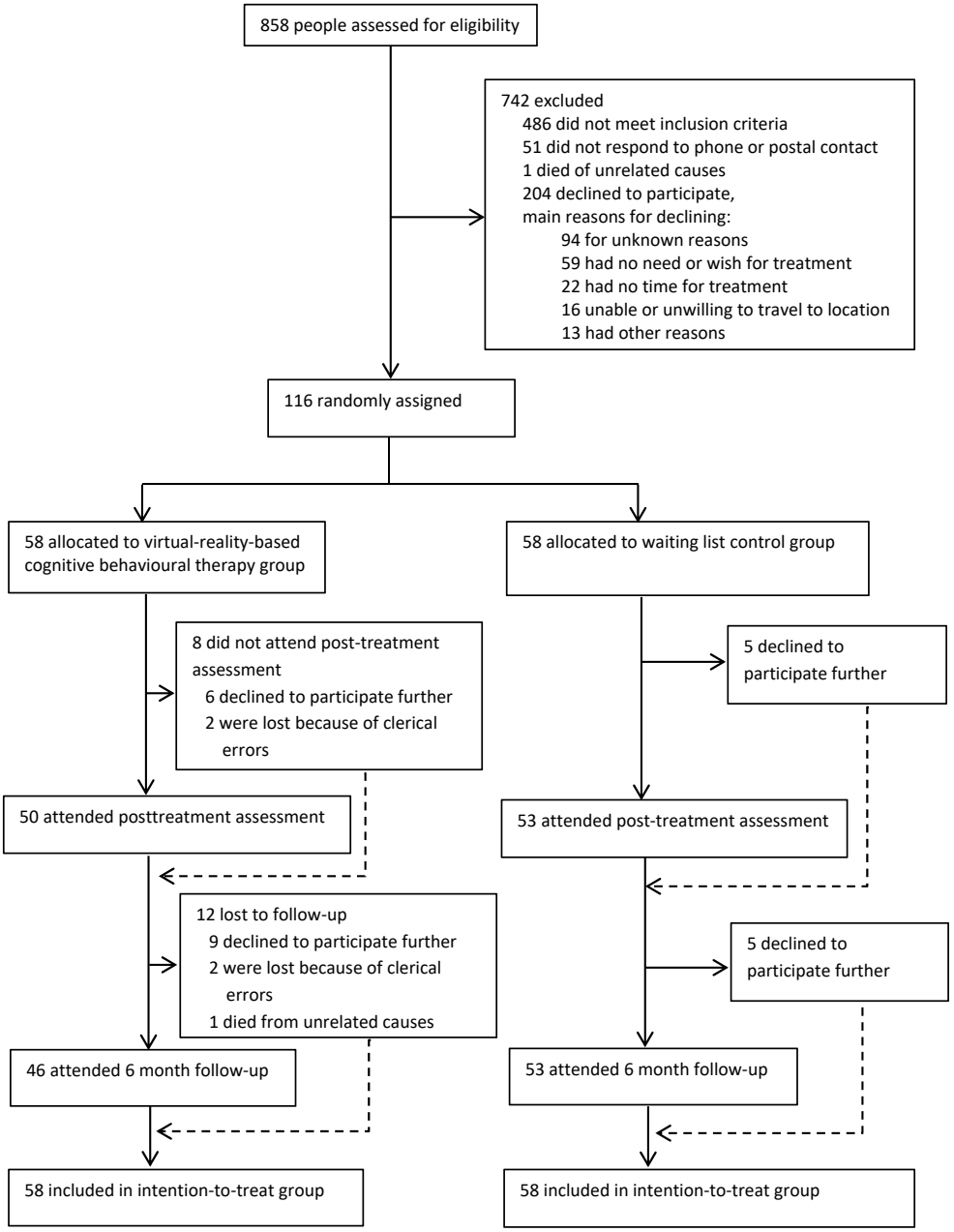

Figure 7.1. Trial flow diagram.
* Specification of participants lost to posttreatment: 6 declined further participation and 2 were lost due to clerical errors by therapist. ‡ Specification of participants lost to follow-up: 9 declined further participation, 1 died of unrelated causes, and 2 were lost due to clerical errors by therapist. First published in Lancet Psychiatry (Pot-Kolder et al., 2018). VR-CBT = virtual reality-based cognitive behavioral therapy.

Baseline characteristics of the sample can be found in table 7.1. Results of costs and outcomes can be found in table 7.2. A small group of participants was responsible for a large portion of the baseline costs, largely related to hospital admissions. The total days of psychiatric admissions were 233 days at baseline, 101 days posttreatment, and zero days at follow-up for the VR-CBT group. The total days of psychiatric admissions were 138 days at baseline, 20 days posttreatment, and 68 days at follow-up for the TAU group.

Incremental effects

Time spent with others

The treatment response rate regarding the time spent with others was 13 patients out of 58 (22%) in the control group and 24 patients out of 58 (41%) in the experimental group. The baseline-adjusted between-group difference between the response rates (i.e., the incremental effect) was 0.23, which was statistically significant (SE = 0.076, t113 = 3.07, 95% CI 0.08–0.38, P = .003).

Table 7.1. Characteristics of the study sample at baseline

	VR-CBT N = 58	TAU N = 58
Male	40 (69%)	42 (72%)
Age in years	36.5 (10)	39.5 (10)
Non-Dutch origin	15 (26%)	25 (43%)
Education		
No/primary	16 (28%)	16 (28%)
Vocational	18 (31%)	24 (41%)
Secondary	9 (16%)	9 (16%)
Higher	15 (26%)	9 (16%)
DSM-IV diagnosis		
Schizophrenia	46 (79%)	49 (85%)
Schizoaffective disorder	1 (2%)	5 (9%)
Delusional disorder	1 (2%)	0 (0%)
Psychotic disorder NOS	10 (17%)	4 (7%)
Duration of illness in years	13.3 (10.6)	14.9 (9.5)
Medication use		
Antipsychotics	54 (93%)	57 (98%)
Olanzapine equivalent of prescribed antipsychotic medication (mg/day)	10.5 (6.8)	11.0 (8.3)
Antidepressants	15 (26%)	17 (29%)
Paid work	8 (14%)	5 (9%)
Safety behaviours	28.8 (14.2)	21.1 (16.0)

Note. Data are n (%) or mean (SD). VR-CBT = virtual reality based cognitive behavioral therapy. TAU = Treatment As Usual. NOS = Not Otherwise Specified. GPTS = Green et al. Paranoid Thoughts Scale. QALY = Quality-adjusted life year. [a] Total three months before baseline. [b] Average costs made per participant three months before baseline, in Euro's 2015.

Table 7.2. Average per participant costs per 3-month period (in € for the year 2015) and average outcomes, by measurement and condition

	Baseline		Post-treatment (3 months)		Follow-up (6 months)	
	VR-CBT	TAU	VR-CBT	TAU	VR-CBT	TAU
Costs, € (SD)						
Healthcare costs	€1,918 (€5,178)	€1,396 (€3,146)	€3,031 (€3,189)	€648 (€960)	€887 (€1,160)	€1,039 (€2,640)
Travel costs	€31 (€23)	€29 (€26)	€60 (€34)	€23 (€15)	€28 (€22)	€24 (€16)
Productivity loss	€553 (€2,730)	€224 (€1,214)	€359 (€1,205)	€214 (€1,127)	€28 (€161)	€102 (€588)
Total (societal) costs	€2,502 (€6,246)	€1,649 (€3,570)	€3,076 (€3,469)	€885 (€1,589)	€943 (€1,185)	€1165 (€2,766)
Outcomes, M (SD)						
GPTS paranoia	85 (34)	77 (31)	70 (31)	75 (31)	67 (33)	75 (33)
Time spend with others	0.416 (0.256)	0.364 (0.266)	0.404 (0.226)	0.323 (0.266)	0.419 (0.209)	0.340 (0.273)
Momentary anxiety	2.986 (1.120)	3.259 (1.484)	2.586 (1.089)	3.221 (1.495)	2.645 (1.095)	3.218 (1.388)
Momentary paranoia	3.064 (1.393)	3.259 (1.418)	2.714 (1.291)	3.221 (1.518)	2.719 (1.293)	3.218 (1.467)

Momentary anxiety

The treatment response rate with regard to momentary anxiety was 17 patients out of 58 (29%) in the control group and 24 patients out of 58 (41%) in the experimental group. The between-group difference between the treatment response rates (i.e., incremental effect) was 0.12, but this difference was not statistically significant (SE = 0.089, t114 = 1.36, 95% CI -0.055 to 0.290, P = .18).

Momentary paranoia

The treatment response rate in momentary GPTS paranoia was 11 patients out of 58 (19%) in the control group and 28 patients out of 58 (48%) in the experimental group. The between-group difference in the response rates was 0.29 and was statistically significant (SE = 0.0841, t114 = 3.48, 95% CI 0.126–0.460, P = .001).

Quality-adjusted life years

The SMD of GPTS paranoia was 0.523, which was statistically significant (SE = 0.120, t114 = 4.37, 95% CI 0.285–0.760, P < .001). Using Sanderson et al.'s conversion factor [14] of 0.1835 and taking into account a follow-up period of half a year, this became a QALY gain of 0.048 (0.523 × 0.1835 × 0.5) favoring the VR-CBT condition and this was statistically significant (SE = 0.011, t114 = 4.37, 95% CI 0.026–0.069, P < .001).

Incremental costs

Incremental health care costs

As can be seen in table 7.2, the average per-patient health care costs in the TAU group was €1,396 at baseline, €648 at posttreatment, and €1,039 at follow-up. The average per-patient health care costs in the VR-CBT group was €1,918 at baseline, €3,031 at posttreatment, and €887 at follow-up. This includes €373.95 per patient for VR-related costs included in the posttreatment costs.

The cumulative costs per patient between baseline and follow-up, including the costs of VR-CBT, were €1,686 and €3,917 in the TAU and VR-CBT conditions, respectively. The between-group difference was €2,231 (€3,917–€1,686) and was statistically significant (SE = 663, t114 = 3.36, P = .001) when not adjusted for the initial cost difference between the conditions at baseline. After adjustment for baseline costs, the incremental health care costs became slightly less at €2,170 and retained statistical significance (SE = 661, t113 = 3.28, P = .001).

Incremental costs stemming from productivity losses

A total of 11.2% (13/116) of the participants had paid work. The average costs stemming from productivity losses per person for the TAU group was €224 at baseline, €214 at

posttreatment, and €104 at follow-up. The average costs stemming from productivity losses per person for the VR-CBT group was €553 at baseline, €359 posttreatment and €28 at follow-up. The cumulative costs per patient between baseline and follow-up were €317 and €387 in the TAU and VR-CBT conditions, respectively. The between-group difference was €70 (€387–€317) and was not statistically significant (SE = 274, t114 = -0.26, P = .80).

Travel costs

The average costs stemming from travel per person for the TAU group was €29 at baseline, €23 at posttreatment, and €24 at follow-up. The average travel costs per person for the VR-CBT group was €31 at baseline, €60 at posttreatment, and €28 at follow-up. The cumulative travel costs per patient between baseline and follow-up were €47 and €88 in the TAU and VR-CBT conditions, respectively. The between-group difference was €41 (€88–€47) and was statistically significant (SE = 6, t114 = -6.73, P < .001).

Incremental costs from the societal perspective

The cumulative societal costs per patient between baseline and follow-up were €2,050 and €4,393 in the TAU and VR-CBT conditions, respectively. The between-group difference was €2,343 (€4,293–€2,050) and was statistically significant (SE = 747, t114 = -3.14, P = .002).

Incremental cost-effectiveness ratios from the societal perspective

The mean incremental costs for a positive treatment responder was as follows:

1. Time spent with others: €2,343/0.23=€10,069.
2. Momentary anxiety: €2,343/0.12=€19,525.
3. Momentary paranoia: €2,343/0.29=€8,079.
4. The mean incremental cost per QALY: €2,343/0.048=€48,868.

Figures 7.2 to 7.4 depict the distribution of the 5,000 bootstrapped ICERs over the cost-effectiveness plane for each of the social participation measures. Figure 7.2 depicts time spent with others, the plane illustrates 99.70% of the ICERs fall in the northeast quadrant, indicating that more treatment responses are gained for higher costs. Figure 7.3 depicts momentary anxiety, the plane illustrates 90.74% of the ICERs fall in the northeast quadrant, indicating that more treatment responses are gained for higher costs. Figure 7.4 depicts momentary paranoia, the plane illustrates 99.74% of the ICERs fall in the northeast quadrant, indicating that more treatment responses are gained for higher costs.

Figure 7.5 depicts the distribution of the bootstrapped ICERs over the cost-effectiveness plane, with the vast majority of the ICERs in the northeast quadrant, indicating that

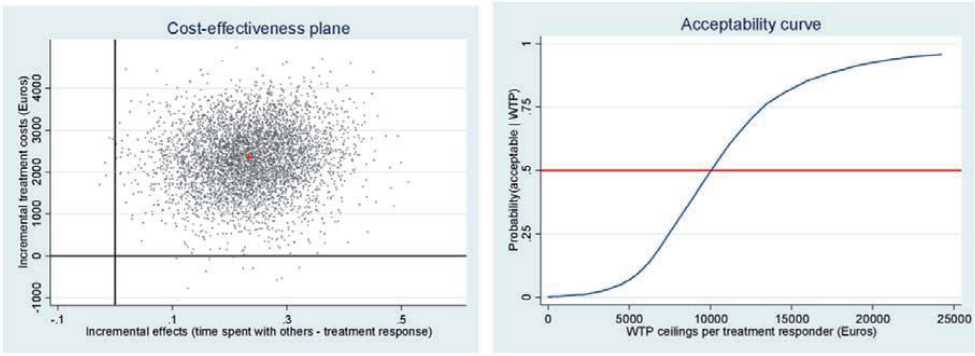

Figure 7.2. Cost-effectiveness plane and willingness to pay (WTP) acceptability curve for time spent with others.

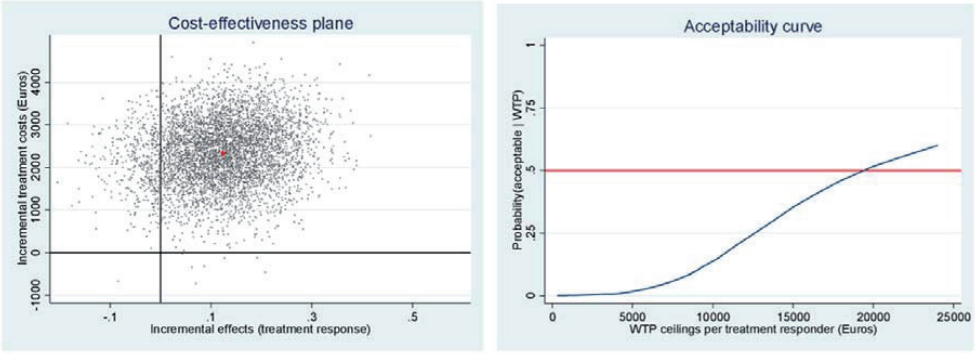

Figure 7.3. Cost-effectiveness plane and willingness to pay (WTP) acceptability curve for momentary anxiety.

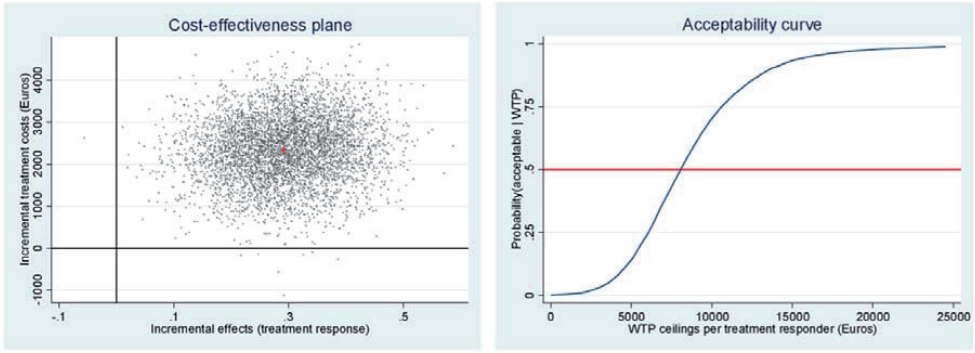

Figure 7.4. Cost-effectiveness plane and willingness to pay (WTP) acceptability curve for momentary paranoia.

more QALYs are gained but for higher costs, while 0.02% of the simulated ICERs fall in the southeast quadrant (i.e., QALY gains for lower costs) for the VR-CBT group compared with the TAU group.

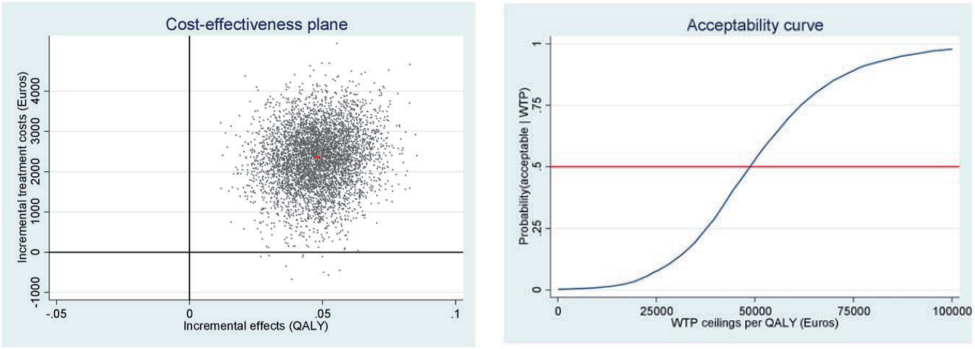

Figure 7.5. Cost-effectiveness plane and willingness to pay (WTP) acceptability curve for quality-adjusted life year (QALY) gain (costs per QALY gained) after 6 months.

Acceptability

The mean incremental cost per QALY was €48,868. When looking at the acceptability curve in figure 7.5, a higher probability that the VR-CBT intervention is deemed cost-effective can also be calculated. For an 80% certainty of cost-effectiveness, the incremental cost for gaining 1 QALY is €66,161, which falls well below the willingness-to-pay ceiling of €80,000 in the Netherlands for a severely disabling condition, such as schizophrenia characterized by paranoid delusions220.

Looking at the three treatment responses, at 50% probability of being cost-effective, the costs are as mentioned: time spent with others, €10,069; momentary anxiety, €19,525; and momentary paranoia, €8,079. Supposing that a decision maker needs an 80% certainty, time spent with others will have to be valued at €14,293 per treatment responder; momentary anxiety at €50,000; and momentary paranoia at €11,342.

Sensitivity analysis

When including safety behavior at baseline as a covariate, the incremental costs per treatment responder on time spent with others became €9,136; momentary anxiety became €17,535; and momentary paranoia became €7,219. When including safety behavior at baseline as a covariate, the incremental costs per QALY gained became €44,597. Overall, incremental costs were somewhat lower when the baseline difference of safety behaviors was included in the analysis.

When including psychiatric admission costs at baseline as a covariate, the incremental costs per treatment responder on time spent with others became €9,729; momentary anxiety became €18,879; and momentary paranoia became €7,750. When including psychiatric admission at baseline as a covariate, the incremental costs per QALY gained became €47,308. Overall, incremental costs were somewhat lower when the baseline difference of psychiatric admission costs was included in the analysis.

When including both psychiatric admission costs at baseline and safety behavior at baseline as covariates, the incremental costs per treatment responder on time spent with others became €8,592; momentary anxiety became €16,597; and momentary paranoia became €6,800. When including both psychiatric admission costs and safety behavior at baseline as covariates, the incremental costs per QALY gained became €42,030. Overall, incremental costs were lower when the baseline differences of both safety behaviors and psychiatric admission costs were included in the analysis.

Discussion

Principal findings

This study aimed to get an impression of short-term cost-effectiveness of VR-CBT for patients with paranoid delusions in comparison to TAU from a societal perspective. Data were collected 6 months after baseline at follow-up. Costs per treatment responder gained were estimated to be between €8,079 and €19,525 for different aspects of social participation, with between 90.74% and 99.74% showing improvement. Cost per QALY gained at follow-up was estimated to be €48,868 with 99.98% showing improved QALYs. Sensitivity analyses showed costs to be lower when baseline differences in both safety behavior and psychiatric admission costs were included in the analysis. Costs per treatment responder gained were then estimated to be between €6,800 and €16,597, with cost per QALY gained at €42,030.

Results in context

How much a society values solidarity with people burdened by disease will determine if guidelines are translated to actual treatment of patients. While the VR-CBT treatment condition is more expensive than TAU only, that was to be expected, as the aim was to add to existing treatment. Results show that this addition improves social participation for people with a psychotic disorder suffering from paranoid ideation. We see this improvement for time spent with others, momentary paranoia, momentary anxiety, and paranoid ideation, via the GPTS.

Engaging in psychological therapy is challenging for many patients suffering from paranoid ideation and treatment results vary. There are several aspects that favor VR treatment. Person-specific behavioral exposure is an important part of increasing treatment effect[187], which is exactly what the interactive VR social environments offer. Patients themselves also prefer VR over in vivo exposure treatment[221] and VR improves treatment motivation for patients[12].

Interestingly, during the follow-up we see that the VR-CBT group resulted in decreased health care costs and decreased costs due to productivity loss compared to the TAU-only

group. There were no psychiatric admission days at follow-up for the VR-CBT group. To determine whether this was a coincidence or a trend, a much longer follow-up period is needed. Short-term societal costs were between €8,079 and €19,525 for a positive treatment response. A disability weight of zero represents no loss of health and a weight of 1 represents health loss equivalent to death[222]. In the Netherlands, the willingness to pay for gaining a QALY ranges between €20,000 and €80,000 but differs per disease[223]. For a severely disabling disease such as schizophrenia, which according to the Global Burden of Disease study 2010 has a disability weight of 0.76, the willingness to pay is €80,000[220,223]. In this context, the VR-CBT treatment that has an ICER of €48,868 per QALY gained can be regarded as acceptable from the cost-effectiveness point of view.

Limitations

The study has several limitations. First, data were collected only 6 months postbaseline. Any longer-term effects and costs are unknown. There are indications that cost-effectiveness for treatment of psychotic symptoms improves with time[224] as health benefits continue. Second, minimal treatment response was set at a 20% symptom reduction. A 20% symptom reduction after just 8 weeks of therapy is clinically relevant in a patient group with an average duration of illness of 14 years with persistently high problematic isolation. Third, VR-CBT was compared to TAU only. The next step would be to compare VR-CBT directly to CBT, which is the current gold standard, as CBT without VR also results in additional costs to TAU. There are, however, also indications that VR-CBT could have positive results in fewer sessions compared to CBT[115]. Comparing VR-CBT directly to CBT also allows for the study of presumed benefits of VR therapy, such as better engagement and the ecological validity of VR on outcome effects. Such a study comparing VR-CBT and CBT on time to response and costs is currently ongoing (Netherlands Trial Register number NL7758). A final limitation was that QALYs were not measured directly. As the EQ-5D (European Quality of Life Five Dimension Scale) was not administered, QALYs were calculated using Sanderson et al.'s conversion factor[214]. Future research needs to include the EQ-5D for direct measurement.

Conclusions

This study found VR-CBT to be cost-effective in the short term from a societal perspective. However, the effect of additional VR-CBT sessions and long-term effects need to be determined while using direct measurement of QALYs.

Supplementary material

Supplementary table S7.1. Direct medical costs

	Price 2015 in Euro
Psychiatrist/Psychologist	112
Training WRAP	Total 560,- *
SPV /Social psychiatric nurse	42.95
Physiotherapist	33
Social worker	65
Daycare GGZ	169
Inpatient clinic	302

Note. Prices are from 2015 and are in Euros. * 8 (sessions) × 2.5 (hours) × 2 (therapists) × 112 (euro per contact-hour) / 8 (participants) = 560 euro. WRAP = Wellness Recovery Action Plan.

8

Chapter 8

Summary and general discussion

Brief summary of main findings

Strengths and limitations

Clinical implications

- Clinical implications of mechanism research
- Virtual reality-based cognitive behavioral therapy for psychotic disorders
- Other virtual reality treatments for psychotic disorders
- Affordability of virtual reality in mental healthcare services
- Evidence-based psychological treatment for patients with psychotic disorders

Future research

- Future research on virtual reality-based cognitive behavioral therapy
- Implementation barriers for virtual reality
- Expecting social contact to be rewarding
- Using virtual reality to improve treatment effects by increasing frequency
- Stand-alone virtual reality-based cognitive behavioral therapy
- New developments
- The future is mixed reality

Brief summary of main findings

This thesis reports on two clinical research studies. The first study researched mechanisms of paranoid ideation, including the ecological validity of virtual reality social environments for eliciting paranoid ideations and behavior, and safety of use concerning cybersickness (chapter 2–4). The second study was a randomized controlled trial examining the effects of virtual reality-based cognitive behavioral therapy for paranoid ideations and social functioning (chapter 5–7).

Chapter 2 explored mechanisms of paranoid ideation using controlled virtual social environments[100]. We found both paranoid thoughts and subjective distress increased in congruence with the degree of social stress added to the virtual social environment. Psychosis liability and pre-existing symptoms positively impacted the level of paranoia and distress in response to social stress. These results provide experimental evidence that heightened sensitivity to environmental social stress may play an important role in the onset and course of psychosis.

Cognitive biases are associated with psychosis liability and paranoid ideation[225]. Chapter 3 investigated the moderating relationship between pre-existing self-reported cognitive biases and the occurrence of paranoid ideation in response to different levels of social stress in a virtual reality environment. Results showed an additive effect of separate cognitive biases on paranoid response to social stress. The effect of social environmental stressors on paranoid ideation is enhanced by attention to threat bias and external attribution bias.

Cybersickness is a negative side effect of virtual reality exposure and is associated with treatment dropout. Chapter 4 aimed to investigate the occurrence of cybersickness[226]. A large majority of patients and controls reported at least one symptom of cybersickness after exposure to the virtual reality environment. Interestingly, many of these physical symptoms were already reported before participants were exposure to the virtual reality environment. This study replicated gender differences in cybersickness symptoms. It also replicated findings that a significant correlation between anxiety and cybersickness can be found in healthy individuals, but not in patients. Anxiety partially mediated cybersickness symptoms, particularly nausea and disorientation. Cybersickness symptoms appear to overlap with anxiety symptoms and are therefore expected to decline during treatment.

The second study was an intervention study. We developed a virtual reality-based cognitive behavioral therapy for patients with a psychotic disorder, which was assessed in a single-blind multisite randomized controlled trial. Chapter 5 outlines the study protocol developed to investigate the effects of virtual reality-based cognitive behavioral treatment on social participation in real life among patients with a psychotic disorder[114]. Chapter 6 presents the main results of the clinical trial[213]. The post-treatment assessment

showed that paranoid ideation and anxiety during real-life social situations were significantly reduced in the virtual reality-based cognitive behavioral treatment group compared with the control group, and these improvements were maintained at the follow-up assessment. According to the post-treatment assessment, virtual reality-based cognitive behavioral treatment did not significantly increase the amount of time spent with other people. The virtual reality-CBT group did show significant improvements in self-stigmatization and social functioning at the follow-up assessment, whereas the control group did not. Safety behaviors and social cognition problems were mediators of change in paranoid ideation. No adverse events were reported relating to the therapy or assessments. Chapter 7 demonstrated that offering virtual reality-based cognitive behavioral treatment to patients with paranoid delusions is an economically viable approach for improving the patients' health in a cost-effective manner[227]. The mean incremental costs for a treatment responder on social participation ranged between €8,079 and €19,525, with 90.74%–99.74% of participants showing improvement. The average incremental cost per QALY was €48,868 over the six months of follow-up, with 99.98% of participants showing improved QALYs.

Real-life symptoms and biases of individual patients occur in virtual reality, and therapy in virtual reality improves the daily life of patients. Virtual reality-based cognitive behavioral therapy is ecologically valid, safe, effective and economically viable for implementation in healthcare for the treatment of patients with psychotic disorders.

Strengths and limitations

The main strength of the ecological validity study described in chapters 2, 3 and 4 is that we used virtual reality as a tool to study interactions between individuals and complex social environments. Environmental studies are complicated by subjective retrospective information about social environments and events. Momentary assessment studies cannot control occurrence of events. This study was the first to experimentally expose individuals to complex social environments with different degrees of social stressors that were completely controlled. The type and degree of environmental stress were both controlled, meaning that all participants were exposed to exactly the same environmental conditions, which would be impossible in a real-life social setting. The use of virtual reality also prevents unintended interaction effects between participants and other people in the social environment, allowing us to study the mechanisms of paranoid ideation which inherently take place in a social context. An additional strength of the first study is the varying degree of liability to psychosis among participants, allowing us to investigate mechanisms over different levels of psychosis liability.

Our second study has all the general benefits of a randomized controlled trial. A particularly important strength of our study is the use of the experience sampling method

to assess the generalization of treatment effects on the daily life of patients. Another strength is the generalizability of the study. The study was carried out in seven mental health centers, and treatment was conducted within the standard healthcare system by regularly employed therapists who received additional training and supervision. Co-morbid diagnoses of the participants were accepted as part of clinical reality. Our results suggest the efficacy and affordability of virtual reality-based cognitive behavioral therapy in real-world conditions, in a sample of patients who are representative of standard clinical practice.

As was already mentioned in the individual chapters, both studies had several limitations. The virtual environments used in both studies were simulated and thus still less complex than real life, which may have reduced ecological validity. In the ecological validity study, there was no condition without any social stressors, i.e. without any virtual people or social noise in the virtual environment. Therefore, it cannot be ruled out that the number of stimuli in virtual reality was more important than the social nature of the stressors. However, the additional effect of avatars' hostile looks compared to a similar environment with neutral avatars does suggests that the social aspect of the stressors matters. In this study, the ultrahigh risk group was small (n = 20), consisted mostly of females and reported more psychotic symptoms than the psychosis group. This may have been because the ultrahigh risk participants were at an earlier stage of their treatment', or because they did not use antipsychotic medication. This may have led to underestimation of the psychosis liability effect on paranoia and distress in virtual reality. Cognitive biases were measured using self-report questionnaires only and were limited to four cognitive biases. Many participants reported little cybersickness and little to none anxiety symptoms, limiting statistical power.

There are three main limitations to the efficacy trial. We did not use an active control group, so we cannot rule out a dose-effect of therapeutic contacts. Secondly, the long-term effects of virtual reality-based cognitive behavioral therapy remain unknown, because follow-up was restricted to just six months post baseline. Thirdly, some eligible patients did not participate, because they were too scared to travel to the therapy location. Thus, our sample might have been biased, because some of the most paranoid and avoidant patients were not able to participate.

Clinical implications

Clinical implications of mechanism research

Both studies discussed in this thesis add to the evidence that is it safe for individuals with psychotic disorders to use virtual reality[12]. No adverse events occurred. Since the experienced cybersickness was partially explained by anxiety symptoms, this is expected

to decrease during treatment.

Multiple studies have now shown that virtual reality can be used reliably to research psychological processes and mechanisms associated with psychosis[228]. This knowledge helps inform clinical practice. Virtual reality offers unique possibilities, such as perfectly controlling and manipulating a social environment. As shown in chapter 2, heightened sensitivity to social stress may play an important role in the development of paranoid delusions. Additional research within this study showed that this heightened sensitivity may be impacted by a history of childhood trauma[229]. Participants with a history of childhood trauma responded to social stressors with more distress, and this effect grew stronger when the level of social stress increased. The effect between social stress and paranoid delusions is moderated by cognitive biases, as shown in chapter 3. When presented with social stress, mentalizing accuracy in individuals with schizophrenia decreased significantly[230]. And following this exposure to social stress, patients reported significantly higher conviction in their paranoid ideas. Psychological treatment for the modification of cognitive biases is called metacognitive training and shows mixed results[110,231]. More effective modification of cognitive biases is needed, as they hinder corrective learning from exposure. Increased understanding of how each specific cognitive bias uniquely contributes to paranoid delusions could improve treatment. We found that both attention to threat bias and external attribution bias increase the strength of the paranoid response to social stress. This suggests that these biases are candidates for targeted clinical interventions when present in an individual patient. Research on the specific effects of exposure interventions and different types of cognitive interventions is needed in regard to paranoid anxiety. As with the treatment of social anxiety, the effects of such separate VR interventions are still unknown[232]. A currently running trial using virtual reality in social cognition training for people with a psychotic disorder might provide a first step towards additional insight[233].

Virtual reality-based cognitive behavioral therapy for psychotic disorders

We found virtual reality-based cognitive behavioral therapy to be very effective in treating paranoid anxiety and improving social functioning in individuals with a psychotic disorder. This is in line with large effects found in a small clinical study[115]. Meta-analysis showed that virtual reality-based cognitive behavioral therapy generates equal effects to regular cognitive behavioral therapy in the treatment of anxiety disorders[188,221]. Since our study compared virtual reality-based cognitive behavioral therapy to treatment as usual only, we do not yet know how it compares financially to regular cognitive behavioral therapy. One hypothesis that has yet to be tested, is that virtual reality-based cognitive behavioral therapy yields clinically relevant treatment effects more quickly. Even if there are some additional costs to virtual reality-based cognitive behavioral therapy, there are several ways in which virtual reality adds value to treatment. Virtual reality is not real, but treatment effects do generalize to real life[234]. And because it is not real,

virtual reality treatment can lower the threshold for patients to start therapy, and for highly anxious patients to participate in exposure and behavioral experiments. Several studies have found that patients prefer virtual exposure therapy to traditional in vivo exposure therapy[155,235]. During our clinical trial, we included several people unable to use public transportation because of anxiety, who were willing to start therapy in our virtual bus. A second advantage of virtual reality-based cognitive behavioral therapy is that it offers more privacy. When helping patients with in vivo exercises, for example in a supermarket, 'the therapist might ask, 'how high', to which the patient answers, '7', talking about their level of anxiety. In a virtual supermarket, the patient stays in the privacy of the therapy room, where patient and therapist can talk about anything and everything that is relevant in that specific situation. This turned out to be a great additional benefit. Instead of having to rely on retrospective information, virtual reality offers the opportunity to discuss thoughts, feelings and behavior as they present themselves. This led to better understanding for both therapist and patient. A third advantage is the ability to give direct feedback to a patient. In virtual reality treatment, the therapist can positively reinforce all adequate behaviors of the patient. At the same time, the opportunity to adjust some behaviors that could have caused problems in real-life turned out to be very helpful. For example, there were a few patients who had lived in social isolation for decades. They would display behaviors in the virtual reality environments that did not match the social context, such as talking extensively about their psychiatric symptoms during a 'small talk' exercise with a stranger in the virtual bus. While sharing this information is appropriate with a mental healthcare professional, we encouraged talking about things such as the weather in the context of small talk with a stranger. Another advantage is that the virtual social environment is completely controlled. The therapist makes sure that certain situations occur to explicitly benefit the patient, while at the same time eliminating the chance of adverse events. Of course, patients do have to be able to deal with unexpected situations in real life. In a later stage of the treatment process, patient and therapist can agree to practice with virtual social situations where the patient does not know the circumstances in advance. A fifth advantage is the opportunity to rehearse. When doing exercises in vivo, interaction occurs within real-world environments. For example, if you do a real-life exercise at the check-out register in a supermarket, the patient interacts with the cashier. Now, imagine that a rehearsal is necessary, then at least a different cashier, or maybe even a different shop is needed. In a virtual supermarket, exercises can be repeated as often as is necessary for the patient. Finally, the greatest advantage of virtual reality is the possibility to personalize treatment based on an individual case formulation as is used in CBTp. Each person has different goals, experiences, levels of anxiety and different 'If…, then…' scenarios to test and explore. Treatment in virtual reality offers the ability to meet these specific personal needs in ways that have never been possible before.

Other virtual reality treatments for psychotic disorders

While the treatment focus of this thesis is cognitive behavioral therapy, literature shows additional promising virtual reality applications for people with a psychotic disorder. Two types of virtual reality treatment for people with a psychotic disorder have been researched: skill training and AVATAR therapy. A review on virtual reality treatment shows promising results in using virtual reality for training vocational skills and job interview skills, though comparisons to an active control condition and larger sample sizes are warranted[6,236]. Virtual reality training can be used to improve social skills such as assertiveness and conversational skills[68,237,238]. Virtual reality cognitive training seems to improve cognitive function[239,240]. Overall, virtual reality offers an interesting and promising therapeutic tool for psychosocial remediation[241].

The AVATAR therapy was developed for people suffering from negative auditory verbal hallucinations. It involves the creation of a digital avatar of their presumed persecutor, voiced by the therapist. The avatar becomes less hostile and concedes power over the course of therapy. A large randomized controlled trial showed that AVATAR therapy was more effective in reducing the severity of verbal hallucinations than supportive counseling, with a large effect size[189]. These findings have since been replicated, observing a strong therapeutic effect on the distress associated with the voices[242].

Affordability of virtual reality in mental healthcare services

While costs of virtual reality hardware and software are declining, they are still substantial. In the Netherlands, health insurers encourage the use of virtual reality treatment by supplying an additional compensation. Currently, therapists need to treat about five people per virtual reality set per day to cover all costs. Anecdotal evidence suggests five virtual reality treatments per day is optimistic. We asked in personal communication Dutch clinical departments, who reported treating about three patients per virtual reality set a day. This means that the mental health institutions need to invest several thousands of euros each year. Since many mental health institutions struggle financially, the willingness to implement virtual reality therapy remains limited, even though institutions are excited about the benefits for patients. It is our hope that further technological developments will reduce hardware costs. In addition, competition in software providers may reduce software costs. Finally, health insurance companies could increase the additional compensation to further encourage the use of virtual reality treatment. When we reach the point that all virtual reality costs are covered by the extra insurance fee, we expect to see a quick rise in implementation of virtual reality treatment in mental healthcare services. Another solution could be to create a transdiagnostic standalone virtual reality center that caters to all patients in a certain region. The Dutch mental healthcare system is divided up into specialized departments, which makes it difficult for each separate department to treat enough patients to cover all costs.

While covering all costs would encourage implementation, having to make additional costs should not be a reason to withhold effective treatment from patients with psychotic disorders. As our study on cost-effectiveness shows, the average incremental cost per QALY (improvement on quality of life) was €48,868 over the six months of follow-up, with 99.98% of participants showing improved QALYs, which means there are additional costs for additional gains in quality of life for patients with a psychotic disorder. This is well below the €80,000 per QALY that the Dutch community is willing to pay for high burdening diseases, according to research[223].

Evidence-based psychological treatment for patients with psychotic disorders

Unfortunately, it is unlikely that many patients will be able to benefit from virtual reality-based cognitive behavioral therapy in the near future. A recent survey in the Netherlands shows that 70 to 75% of patients with a psychotic disorder do not have access to any form of cognitive behavioral therapy for psychosis[243]. Over 50% of cognitive behavioral therapy for psychosis is provided by underqualified therapists. The survey even shows a decline in the number of patients with a psychotic disorder receiving cognitive behavioral therapy for psychosis over the past five years, from 4% down to 2.5%. According to the survey, most patients have not been offered treatment according to the clinical guidelines, which is unconscionable, and national efforts should be made to increase accessibility. Once a therapist is qualified to provide cognitive behavioral therapy, learning how to use virtual reality is only a small step. But the clinical implementation of (virtual reality-based) cognitive behavioral therapy will be an ongoing challenge in the Dutch mental healthcare system.

Future research

Future research on virtual reality-based cognitive behavioral therapy

Future research should compare virtual reality-based cognitive behavioral therapy with standard cognitive behavioral therapy in terms of treatment effects and cost-effectiveness. Longer follow-up periods are needed to see if therapy effects are retained. Furthermore, virtual reality-based cognitive behavioral therapy should be investigated as a stand-alone therapy and not just as an add-on to antipsychotic medication. Several recent trials suggest that cognitive behavioral therapy without medication may be a safe and acceptable option for people with psychosis[39,244]. The ecological validity study showed virtual reality to be safe for patients with an ultrahigh risk of developing psychosis. Efficacy of virtual reality-based cognitive behavioral therapy should be investigated in these patients as well, especially since the use of antipsychotic medication is not recommended for ultrahigh risk patients[245,246]. A proactive cognitive behavior therapy intervention for high risk patients resulted in a 50% risk reduction (and 43% at 48

months after baseline)[247,248]. The intervention was effective and cost-saving at both the 18- and 48-months follow up, averting psychosis and increasing Quality Adjusted Life Years (QALYs)[248,249]. While these are great results, it also means that many patients did make the transition to a psychotic disorder. Important predictors for transitioning were subjectively experienced social marginalization, decline in social functioning, and distress associated with suspiciousness[248]. This profile opens up the possibility of personalizing the treatment intensity for this subgroup, focusing on improving social functioning, for which VR-CBT is a promising treatment.

A meta-analysis of randomized controlled trials for virtual reality exposure therapy for anxiety and related disorders showed that virtual reality exposure therapy and in vivo exposure therapy did not have significantly different effect sizes[221]. However, virtual reality could prove to be useful in improving therapy outcomes. Looking at developments to better understand the mechanisms of change of cognitive behavioral therapy, virtual reality could help maximize exposure therapy by actively making use of elements such as expectancy violation, deepened extinction, variability and the use of multiple contexts[41]. According to research by Craske[41,250], there are several ways in which virtual reality could support long term effects of therapy. By offering many variations of conditioned stimuli, and by offering multiple conditioned stimuli at the same time, the learning effect should become stronger (deepened or compound learning). That should lower chances of renewal of fear. A study using virtual reality for treating spider phobia indeed found that variation in context during exposure reduced post-treatment return of fear, and variation in stimuli during exposure had short term and long term beneficial effects on treatment outcome[251].

In the Netherlands, an increasing number of commercial companies is already offering 360-degree videos as 'evidence-based' virtual reality-based cognitive behavioral treatment. However, no research has been conducted yet on 360-degree virtual reality videos for cognitive behavioral treatment. All current scientific research focusses on interactive computer-generated virtual environments. Many of the advantages of virtual reality-based cognitive behavioral treatment, such as personalization and interaction, are not applicable to 360-degree videos. While these 360-degree videos often offer several 'levels' of difficulty, this cannot be compared to specifically tailoring the environment to a patient. Furthermore, 360-degree videos are not able to interact in real-time with the patient, making it a more passive experience. A study in healthy controls shows that active virtual reality scenarios are more effective in eliciting social anxiety than passive virtual reality scenarios[252]. Overall, we expect the effects of 360-degree videos to be less than the effects of interactive computer-generated virtual environments for virtual reality-based cognitive behavioral therapy. The one exception could be the use of personalized 3D-video, i.e. filming a specific situation that is important and relevant for that individual in 360 degrees. In one proof-of-concept study among students,

a stereoscopic 360-degree camera was used to record an important personal event, showing that such personal recordings are feasible, though any effects are still unclear[253]. Unfortunately, filming personal virtual exposure environments for each patient would be costly and time-consuming.

Further research is needed to explore the additional possibilities of using virtual reality to improve therapy outcomes. For example, what are the effects of actively combining interoceptive exposure (such as hyperventilation exercises) and in vivo exposure (for example, wearing a warm coat and heavy bag) with virtual reality environments such as a virtual bus. All currently available knowledge on treatment and diagnostics can be used in virtual environments as well. But we should investigate the separate effects. We could also try to improve outcomes by offering the feared outcome. For example, we treated a patient who was afraid the cashier would comment on him being too slow and having shaking hands. First, we practiced the natural situation, with the patient being himself and the cashier remaining nice. Then we practiced the patient being intentionally slow and shaky, with the cashier remaining nice and professional. Finally, we practiced with the cashier behaving unprofessionally and commenting on the speed and shakiness of our patient. The patient learned during the therapy that he was less slow and shaky than he anticipated. He also learned that if he was slow and shaky, most cashiers stay nice and professional. Lastly, the patient learned that, while unpleasant, he was able to tolerate the feared outcome of a mean cashier and did not have a nervous breakdown! A final thought on future virtual reality-based cognitive behavioral therapy has to do with the emotion regulation strategy of 'affect labeling'. During the treatment sessions, we found it very valuable to be able to explore and label thoughts and feelings experienced in real-time together with the patient. During this process, patients improved their knowledge of symptom dynamics, which were often overwhelming and confusing before.

Implementation barriers

The use of virtual reality will require some therapists to change their mindset. In current clinical practice, behavioral experiments and exposure exercises are mostly prepared during the session, while the patient is expected to perform these on their own between sessions. When virtual reality becomes available during sessions, therapists will need to adapt to more behaviorally active sessions. The use of advanced technology during therapy might also be a challenge for some therapists. Until recently, with the COVID-19 pandemic necessitating E-health[254] use, therapists were not used to technology being part of therapy. Many evidence-based E-health-developments in therapy have proved hard to implement thus far[255]. Factors proven to be important for E-health implementation were: the individual e-health technology, the outer setting, the inner setting and the individual[256]. The lack of acceptance by health professionals is one of the most important barriers[257]. However, little is known about the barriers specific to virtual reality therapy. Anecdotally, in our experience, there was a specific group of therapists who really

embraced virtual reality-based cognitive behavioral therapy. These therapists were used to interacting with technology in their own daily life. Many took initiative to become trained in virtual reality treatment. Additionally, we saw that this group was already practicing active exposure and behavioral experiments during their regular cognitive behavioral therapy sessions. Many were either certified cognitive behavioral therapists or in training for certification. Thus, we can also look at virtual reality-based cognitive behavioral therapy as an attractor and a way to get more trained therapists excited about working in the field of psychosis. However, research on implementation barriers for virtual reality therapy is needed to move beyond anecdotal experience.

Using virtual reality to increase treatment frequency

Frequency of treatment sessions is a variable for treatment effect, but research on this subject is surprisingly limited. In clinical practice in the Netherlands, the most common therapy frequency is one forty-five-minute session a week. However, clinical effect trials generally offer two sixty-minute therapy sessions a week, as was the case with the Dutch trial on virtual reality for social phobia[258] and the virtual reality-based cognitive behavioral therapy trial we conducted ourselves. The discrepancy between therapy frequency in research and in clinical practice can have many reasons. Availability of the therapist, session costs per week, and patients having to make time in their calendars all play their part. Recent research on depression shows that two therapy sessions a week generate a better therapy effect than the same amount of sessions (up to twenty) delivered once a week, for both cognitive behavioral therapy and interpersonal psychotherapy[259]. For the treatment of PTSD, intensive short-term therapy is becoming increasingly common in the Netherlands, and one study found that 73% of patients recovered from PTSD after a 7-day intensive treatment[260]. For anxiety and related disorders such as paranoid anxiety, little research exists in which weekly sessions are directly compared to multiple sessions a week while controlling for dose response. One study found that twelve session behavioral therapy for social anxiety was more effective when delivered in twelve weeks instead of eighteen weeks[261]. What therapy effects would we find when creating a 7-day program combining in vivo therapy with virtual reality treatment? Or when we complement weekly face-to-face therapy sessions with virtual reality-exercises that the patient can do at home, in the comfort of their own space, at a time of their own choosing and without the therapist. Further research is needed to better understand and employ the clinically relevant treatment effect variable of frequency. Virtual reality, in particular, could play a part in this.

Stand-alone virtual reality-based cognitive behavioral therapy

Not everyone can afford to go see a therapist for psychological treatment. In countries like the Netherlands, psychological treatment is often covered by health insurance, but waiting lists are a persistent problem. If stand-alone virtual reality-based cognitive

behavioral therapy could replace the therapist, this would make psychological therapy more readily available for many people. While there are initial development costs, implementation on personal consumer hardware should keep overall costs per person low if many people get access to the treatment. For relatively simple psychological disorders, i.e. specific phobia's such as fear of heights and fear of spiders, stand-alone virtual reality treatments are already being developed. ZeroPhobia is a fully self-guided, phone app-based virtual reality cognitive behavior therapy for fear of heights, using cardboard virtual reality goggles. ZeroPhobia showed large symptom reduction after three months[262]. OxfordVR is also dedicated to developing automated treatments, using a virtual coach. They currently offer programs for fear of heights[263] and for social engagement. A similar program, called the GameChange project, is being developed for psychosis, consisting of a six-session automated treatment that will be compared to standard treatment in a clinical trial[264]. In the THRIVE-study, patients with persistent persecutory delusions in the context of non-affective psychosis will be randomized across four 30-minute sessions of either automated virtual reality cognitive treatment or virtual reality mental relaxation[265].

A second way in which virtual reality stand-alone treatment could replace a therapist, is by using it as a relapse prevention tool for more complex psychological disorders. During the initial face-to-face sessions, the therapist and the patient develop an individual case formulation and matching therapy. With complex disorders, this is an essential step. During the subsequent virtual reality-based cognitive behavioral therapy, patients learn to become their own therapist as much as possible, better understanding their symptom dynamics and how to manage them, thus making the therapist redundant. Unfortunately, relapse is common after therapy. Despite the positive effects of exposure treatment for anxiety, 19 to 62% of patients experience some form of relapse[250]. If patients would have access to virtual reality at home after therapy to continue practicing or to fall back on in case of recurring symptoms, this could prove to be very helpful, both to deepen extinction and to prevent a (full) relapse. Patients would not be dependent on availability of a therapist, but can use their knowledge to practice autonomously and immediately. For this option to become readily available in the future, two conditions need to be met. Firstly, virtual reality hardware needs to become a common household item, or at least easy and inexpensive to obtain when needed. Secondly, patients should be able to download the virtual reality software online, as is already common in the gaming industry. The software should allow patients to create automated virtual scenarios to practice with. Developing several automated scenarios in advance, together with the therapist, can become part of the treatment protocol. Since no such automated virtual tool is available yet, more basic options can be explored, such as the use of the free Google Cardboard Camera-app. This app takes a 360-degree 3D picture and can be downloaded on any smartphone. For example, when one of our patients had a relapse in social anxiety, we used this app to create 360-degree 3D pictures of her daytime activity

center. With a cardboard viewer and her own smartphone, she could at least practice being in her own social environment to some extent. Such methods require additional research. As mentioned, there is a lack of research on the effect of virtual reality-based cognitive behavioral therapy using 360-degree movies, let alone still images.

Since artificial intelligence keeps evolving, in the future, it might even become possible to develop full stand-alone virtual reality treatment for more complex psychological disorders. Artificial intelligence could then support the patient in the process of developing their individual case formulation and could coach therapy sessions, all in the safety and comfort of their own home. Two projects are worth mentioning here. The first is a project developing a virtual agent that assists in post-traumatic stress disorder therapy[266,267]. Personalization of the agent's feedback messages was found particularly important when symptoms were getting worse. For example: '*I see you indicate that your complaints have gotten substantially worse (note rising symptoms). I'm sorry to hear that (empathy). However, it's always hard work before we see any results (give perspective). Hold on! (motivation).*' Personalization of messages also motivated the patient to continue therapy and improved their trust in a good therapy outcome. Artificial intelligence is what could transform standardized stand-alone virtual reality treatment into personalized stand-alone virtual reality treatment. As research has shown, personalization is an important tool for outcome effect[37]. A second project worth mentioning is Ellie, a virtual human developed by the University of Southern California's (USC) Institute for Creative Technologies. Ellie mimics a real therapist in motion, speech and actions. The virtual human conducts a fully automated, semi-structured screening interview with a single user via spoken language. An analysis of face-to-face interviews informed the creation of an AI that was ultimately fully-automated. The Computer Expression Recognition Toolbox (CERT) automatically detects facial actions, including expressions of basic emotions such as sadness. This information is used to determine Ellie's response[268]. While some patients will prefer a real therapist, it seems that at least a subgroup of patients would prefer the virtual therapist. In a study with virtual human Ellie, participants who believed they were interacting with a computer reported lower fear of self-disclosure, lower impression management, displayed their sadness more intensely and were rated by observers as more willing to disclose than participants who believed they were interacting with a human[269]. A new version of Ellie as a mobile phone app is also in development, using self-report and wearable devices for biofeedback to inform the virtual human AI[270].

In conclusion, stand-alone virtual reality could replace psychological treatment given by a therapist for relatively simple disorders in the near future. It does seem likely that more virtual reality treatments will become fully automated and will even become available as apps. Using stand-alone virtual reality to treat more complex disorders poses two main challenges. Firstly, a therapist is still needed to develop an individual case formulation and personal treatment plan. Developing the individual case formulation

is an interactive process, where patient and therapist discover the personal dynamic of the symptoms and safety behaviors together. Secondly, when the therapeutic exercises involve complex social interactions, a therapist is needed to role-play the virtual person in real-time in order to respond to the behavior of the patient. While the development of artificial intelligence could provide more stand-alone options in the future, these are still quite a way off for treatment of the most complex disorders. However, the aforementioned GameChange project is taking a first step in this direction, and it will be very interesting to see if this generates clinical results.

Expecting social contact to be rewarding

One of our findings was that the amount of time spent with other people did not increase following the reduction of paranoid ideation and anxiety in social situations. This may be because the time period was too short for this behavior to develop. At the follow-up, we did find a significant increase compared to the control condition. However, data showed that this was affected by the control condition deteriorating and spending less time with other people. The average duration of illness was fourteen years, and many patients had a very limited social network outside of healthcare professionals. But even if patients no longer fear social situations (signal learning during exposure exercises), that does not automatically mean that they find them pleasurable (evaluative learning of the positive or negative valence of a stimulus)[271]. Fear of people disappears, but that does not imply that they start expecting social contact to be positively rewarding, or that they now like people more and prefer to be in their company more often. This could explain why we found no change in the factor 'perceived social threat', since this factor was about enjoying company and feeling accepted. Research on the subjective experience of paranoid ideation points to multiple sub-themes that are relevant for patients[272], identifying possible virtual reality-based cognitive behavioral therapy focus, for example, helping people to feel a sense of belonging in social settings, or teaching them additional social skills to feel more certain about how to interact with other people. When social interactions become positively reinforced by a sense of belonging and when feelings of social competence increase, this might encourage future social interactions.

New developments

New technologies related to virtual reality are developing rapidly. One technological development is augmented reality. Augmented reality is defined by Merriam-webster as: 'an enhanced version of reality created by the use of technology to overlay digital information on an image of something being viewed through a device (such as a smartphone camera)'. This device can be a smartphone (think 'Pokémon Go'), an augmented reality headset or augmented glasses you can wear outside, such as Google Glass. Using an augmented reality headset indoors does not seem to add value over using a virtual reality headset. The virtual reality headset actually offers more options,

as part of its strength is that it allows patients to travel to different places without leaving the therapy room. Augmented glasses do offer interesting additional features for therapeutic purposes. The person wearing the glasses can be presented with an additional layer of information, while experiencing this additional layer in private. In theory, a virtual therapist or coach could be developed, supporting an individual in difficult real-life situations. Biofeedback could be used to inform the artificial intelligence on how anxious or calm the patient is. A great benefit of using virtual reality-based cognitive behavioral therapy is that the therapist can team-up with the patient in real-time during difficult virtual situations. Augmented glasses may help to bring this benefit to real-life situations. When biofeedback shows increased anxiety, the virtual therapist could say something similar to the aforementioned personalized messages[267]: '*I see your anxiety is rising (acknowledgement). I'm sorry to see that (empathy). However, that's completely normal and means you are doing the hard work to get results (give perspective). Hold on, you can do this! (motivation).*'

Another development to keep an eye on, is virtual switching of body and perspective. Researchers on eating disorders have been working with virtual body experiences for a while[273]. This embodiment experience of feeling one with the virtual body happens within five seconds, and it is suggested that this feeling of embodying a virtual body seen from a first-person perspective happens by default in virtual reality[274]. Experiencing a virtual body changes a person's body image[275]. In addition to swapping with a virtual body, it is also possible to swap perspectives. Patients can thus experience a virtual social scenario from multiple perspectives, increasing understanding of that virtual social scenario. Using a first-person perspective in virtual reality also allows a person to walk a mile in someone else's shoes. For example, Auti-Sim is a virtual reality experience of sensory overload as experienced by people with autism spectrum disorder. After the experience, participants reported increased emotional concern, helping intentions, and willingness to volunteer compared with an observation-only or text vignette intervention[276]. A similar anti-stigma virtual experience could be used for psychotic experiences. The virtual reality experience app 'the confused man' (in Dutch: De verwarde man, see addendum 1) is a good example of this, as is Labyrinth Psychotica (see addendum 2). Although these experiences have not (yet) been researched, user responses are positive. Research also shows that when offenders have experienced a victim's perspective in virtual reality, they show improved emotion recognition afterwards[277]. Another study confirms that a virtual reality perspective swap increases pro-social behavior via cognitive perspective of the other person, an important part of empathy[278]. A virtual reality study on sexual harassment examined the effects of offering some male participants the experience of both the female victim and of being in the group of male offenders, while other male participants were only offered the experience of being in the group of male offenders. Compared to both the neutral control group and the offenders-only group, those who had experienced the perspective of the female victim administered less shocks to a female

in a virtual reality version of Milgram's obedience experiment a week later. However, those who only experienced the virtual perspective of the male offender administered more shocks to a female compared to both the control group and the victim perspective group[279]. While this study underlines the possible impact of experiencing a virtual perspective, it also reminds us to be cautious of creating unwanted or even harmful effects.

An element of the full body illusion that is tentatively explored, is the addition of touch. Affective touch, when synchronized with a virtual experience of touch, enhances the full body illusion. Affective touch is important in social interactions with family and social groups and elicits feelings of comfort and pleasure in people of all ages[280]. However, affective touch is rated as less pleasant by people with autism spectrum disorder and by people who have experienced childhood trauma[281]. Being touched is an important part of our social reward system and can affect our mental health. Adding touch to virtual embodiment in social environments could help explore those mechanisms, starting with the effects of interpersonal traumatization and sensory sensitivity, because these could influence the social experience for people with a psychotic disorder, since they are highly likely to have had traumatic experiences in the past[16].

The future is mixed reality

Virtual reality brings daily life into the therapy room, while experience momentary sampling technology measures psychological phenomena in their natural context. Technology continues to close the gap between the real life of patients and the therapy room. This coincides with the growing importance of technology and multimedia realities in western society. The recent unforeseen COVID-19 pandemic has acutely accelerated the use and implementation of E-health in mental healthcare and may prove to be a turning point[254].

The meaning and construction of reality has always been a fascinating subject for both philosophers and scientists. What is true? What is real? What can we know? And now, this construction of reality is rapidly changing. The future is one of mixed reality (XR); of virtual, augmented, online and physical realities. Mixed realities challenge our understanding of a shared reality as humans, and both therapists and scientists will need to expand their boundaries. As writer William Gibson states: "*Cyberspace is everything. It's interpenetrating our everyday reality to the point that on-line is our normal waking state*".

Addendum 1. De verwarde man

De Virtual Reality Ervaring *De Verwarde Man* is gemaakt om mensen te laten ervaren hoe het is om een psychose te hebben. Tijdens de workshop met deze VR-ervaring ontdek je al snel dat de grens tussen gezond en verward gedrag niet zo helder is en dat een psychose iedereen kan overkomen.

Door je de psychose te laten ervaren, slaat initiatiefnemer Jeroen Zwaal een brug tussen het geschetste beeld in de media en de werkelijke psychose-ervaring.

Als je door de VR-bril van de psychotisch kwetsbare medemens hebt gekeken, krijg je meer begrip voor het verwarde gedrag. Tevens wordt duidelijk dat een psychose een tijdelijke staat is, waardoor het inzichtelijker wordt dat er naast al het leed er ook een goed leven mogelijk is met een psychotische kwetsbaarheid.

Bron: vrdeverwardeman.nl

Addendum 2. Labyrinth psychotica

Labyrinth Psychotica provides artistic psychosis simulation workshops with THE WEARABLE and THE LABYRINTH that simulate 33 subjective experiences of psychosis.

DO-IT-YOURSELF PSYCHOSIS

Labyrinth Psychotica has dedicated the last 14 years to researching, developing, building, and helping people learn about psychosis in the most direct way: through the senses. Labyrinth Psychotica forms a bridge between theoretical knowledge and practical experience of psychosis. We not only inform and educate about psychosis we also stimulate individual imagination by our unique 'DO-IT-YOURSELF' workshop design.

Source: www.labyrinthpsychotica.org

9

Chapter 9

Dutch summary, acknowledgements, curriculum vitae and publications

Samenvatting (Dutch summary)

Korte samenvatting van de belangrijkste bevindingen

Dit proefschrift rapporteert over twee klinische onderzoek studies. De eerste studie onderzocht mechanismen van paranoïde wanen, inclusief de ecologische validiteit van virtuele sociale omgevingen voor het uitlokken van paranoïde gedachten en gedrag, het de veiligheid van gebruik omtrent het optreden van cyber sickness (Hoofdstuk 2–4). De tweede studie was een gerandomiseerd klinisch onderzoek naar de effecten van in virtual reality gebaseerde cognitieve gedragstherapie voor paranoïde wanen en sociaal functioneren (Hoofdstuk 5–7).

Hoofdstuk 2 onderzocht mechanismen van paranoïde wanen en maakte daarvoor gebruik van gecontroleerde virtuele sociale omgevingen[100]. We vonden dat zowel paranoïde gedachten als subjectieve spanning toenamen in overeenstemming met de hoeveelheid sociale stress die aan de virtuele sociale omgeving werd toegevoegd. Psychose gevoeligheid en reeds bestaande symptomen hadden een positieve invloed op de mate van achterdocht en stress die mensen ervaarde in reactie op de sociale stress. Deze resultaten geven experimenteel bewijs dat een verhoogde gevoeligheid voor sociale stress een belangrijke rol speelt in het ontstaan en het beloop van psychotische stoornissen.

Cognitieve biases zijn geassocieerd met psychose gevoeligheid en paranoïde wanen[225]. Hoofdstuk 3 onderzocht de modererende relatie tussen reeds bestaande zelf-gerapporteerde cognitieve biases en het optreden van paranoïde gedachten in reactie op verschillende niveaus van sociale stress in een virtuele sociale omgeving. De resultaten lieten een additief effect zien van de verschillende cognitieve biases op de mate van paranoïde response bij sociale stress. Dus hoe meer verschillende cognitief biases er bij één persoon aanwezig waren, des te sterker de paranoïde respons op sociale stress. Daarnaast lieten de resultaten dien dat bij de aanwezigheid van de cognitieve biases 'Aandacht voor gevaar' of 'Externe attributie' mensen een versterkte paranoïde respons gaven in reactie op sociale stress.

Cybersickness is een negatief bijeffect van bloostelling aan virtual reality omgevingen, en het optreden ervan is gerelateerd aan het stoppen met virtual reality therapie. Hoofdstuk 4 onderzocht het optreden van cybersickness[226]. Een grote meerderheid van de deelnemers rapporteerde tenminste één symptoom van cybersickness nadat ze waren blootgesteld aan de virtual reality omgeving. Wat opviel was dat een groot deel van deze symptomen vooraf ook al gerapporteerd werden, dus nog voordat de deelnemers waren blootgesteld aan een virtual reality omgeving. Deze studie repliceerde gender verschillen in het optreden van cybersickness symptomen, waarbij vrouwen meer cybersickness symptomen rapporteren, ook al vooraf aan de blootstelling aan de virtual reality omgeving. Het onderzoek repliceerde ook dat een significante relatie tussen angst en cybersickness symptomen wel gevonden wordt bij deelnemers met een lage psychosegevoeligheid ('gezonde controles'), maar niet bij deelnemers met een

hoge psychosegevoeligheid. Mogelijk kan dat worden verklaard omdat deelnemers met een hoge psychose gevoeligheid vooraf al veel meer symptomen van cybersickness rapporteerde. Angst bleek een gedeeltelijke mediator voor het optreden van cybersickness symptomen, vooral voor misselijkheid en desoriëntatie symptomen. Het lijkt er op dat cybersickness symptomen overlappen met de symptomen die optreden bij angst. De verwachting is daarom ook dat als de angst gedurende een virtual reality therapie afneemt, de gerapporteerde cybersickness symptomen ook een daling zullen laten zien.

De tweede studie van dit proefschrift was een interventie onderzoek. We ontwikkelden een in virtual reality gebaseerde cognitieve gedragstherapie voor patiënten met een psychotische stoornis. De therapie is onderzocht in een enkel-blind gerandomiseerde gecontroleerde multicenter onderzoekstudie.

Hoofdstuk 5 beschrijft het studie protocol dat werd ontworpen om het effect te onderzoeken van de therapie op sociale participatie in het dagelijks leven van patiënten met een psychotische stoornis[114].

Hoofdstuk 6 presenteert de belangrijkste resultaten van de klinische onderzoekstudie[213]. De meting na de virtual reality therapie liet een significante afname zien van paranoïde gedachten en angst tijdens sociale situaties in het dagelijks leven, vergeleken met de controle groep die de behandeling niet had gekregen. Deze verbeteringen bleven bestaan bij de follow-up meting. De meting na de virtual reality therapie liet geen significante toename zien van de hoeveelheid tijd doorgebracht met andere mensen. Bij de follow-up meting was er wel een significante toename van de hoeveelheid tijd doorgebracht met andere mensen ten opzichte van de controle groep, alleen liet de ruwe data zien dat dit vooral kwam doordat de controle groep minder tijd was gaan doorbrengen met andere mensen. De groep die de virtual reality behandeling heeft gekregen liet verder bij de follow-up meting een significante verbetering zien van sociaal functioneren en een afname van zelf-stigmatisering, terwijl de controle groep geen verbeteringen liet zien. Veiligheidsgedrag (bijvoorbeeld vermijden of vluchten) en problemen met sociale cognitie waren mediatoren van verandering in de paranoïde symptomen. Er traden bij de metingen en bij de behandeling geen ongewenste onbedoelde effecten (adverse events) op.

Hoofdstuk 7 toonde aan dat het aanbieden van in virtual reality gebaseerde cognitieve gedragstherapie aan patiënten met paranoïde wanen een economisch vatbare benadering is voor het verbeteren van de gezondheid van patiënten met een psychotische stoornis op een kosteneffectieve manier[227]. De gemiddelde incrementele kosten voor een behandeleffect op sociale participatie bedroeg tussen de €8.079 en €19.525, waarbij 90,74%–99,74% van de patiënten een verbetering liet zien. De gemiddelde incrementele kosten per QALY (Quality-adjusted life year) bedroeg €48.868 over de 6 maanden tot en met de follow-up, waarbij 99,98% van de patiënten een verbetering liet zien.

Over het algeheel kan worden gezegd dat symptomen en cognitieve biases die mensen in het dagelijks sociale leven hebben, ook optreden in virtuele sociale omgevingen. Virtual reality kan goed worden gebruikt voor wetenschappelijk onderzoek naar (sociale) mechanismen zoals die van paranoïde wanen. Omgekeerd, zorgt een behandeling in virtuele sociale omgevingen voor verbeteringen in het dagelijks leven van patiënten met een psychotische stoornis die last hebben van angst en achterdocht. In virtual reality gebaseerde cognitieve gedragstherapie is ecologisch valide, veilig, effectief en economisch verantwoord voor implementatie in de gezondheidszorg voor de behandeling van patiënten met een psychotische stoornis.

Sterke punten en beperkingen

Het belangrijkste sterke punt in het onderzoek naar mechanismen en ecologische validiteit in hoofdstuk 2, 3 en 4 is dat we gebruik hebben gemaakt van virtual reality als een middel om onderzoek te doen naar interacties tussen individuen en complexe sociale omgevingen.

Omgevingsstudies worden gecompliceerd door subjectieve retrospectieve informatie over sociale omgevingen en gebeurtenissen. Ecologische steekproef studies (ESM) kunnen wel metingen doen in de sociale omgeving, maar hebben geen invloed op het optreden van gebeurtenissen. Deze studie was de eerste die deelnemers experimenteel blootstelde aan complexe sociale omgevingen met diverse niveaus van sociale stress die compleet gecontroleerd waren. Zowel het type sociale stress als de mate van sociale stress werden gecontroleerd, waardoor alle deelnemers blootgesteld werden aan exact dezelfde omgevingsfactoren. Dat zou volstrekt onmogelijk zijn in echte dagelijkse sociale omgevingen. Het gebruik van virtual reality voorkwam ook onbedoelde interactie effecten tussen deelnemers en andere mensen in de sociale omgeving, wat ons in staat stelde de mechanismen van paranoïde wanen te bestuderen welke inherent plaatsvinden in een sociale context. Een ander sterk punt van de eerste studie is ook het onderzoeken van deelnemers met verschillende maten van gevoeligheid voor psychose, waardoor we mechanismen onderzoek konden doen over verschillende niveaus van psychosegevoeligheid heen.

Onze tweede onderzoek heeft de algemene voordelen die gepaard gaan met een gerandomiseerde gecontroleerde studie. Een sterk punt specifiek voor deze studie is het gebruik van de Experience Sampling Methode naar de generalisatie van behandeleffecten naar het dagelijks leven van de deelnemers. Een ander sterk punt is de generaliseerbaarheid van de studie. De studie is uitgevoerd in de dagelijkse praktijk van zeven GGZ instellingen, en uitgevoerd door de psychologen in dienst van de instelling met een aanvullende training en supervisie. De inclusiecriteria waren ruim; alle co morbiditeit aan klachten en classificaties van deelnemers werden geaccepteerd als de klinische realiteit. Daarmee laten onze resultaten het effect en de betaalbaarheid zien van in virtual reality gebaseerde

cognitieve gedragstherapie in realistische omstandigheden, bij een groep patiënten die representatief zijn voor de dagelijkse klinische praktijk.

Zoals ook eerder beschreven in de losse hoofdstukken, hebben beide studies verschillende beperkingen. De virtuele sociale omgevingen die zijn gebruikt bij beide studies zijn gesimuleerd en daarmee minder complex dan het echte leven, wat de ecologische validiteit beperkt kan hebben.

In de eerste studie naar mechanismen en ecologische validiteit was geen conditie opgenomen zonder enige sociale stressoren, ofwel zonder enige virtuele mensen of sociaal achtergrond geluid in de virtuele omgeving. Daardoor kan niet worden uitgesloten dat het aantal stimuli in de virtuele omgeving belangrijker was dan de sociale aard van de stressoren. Echter, het additionele effect van de boze gezichtsuitdrukkingen vergeleken met dezelfde omgeving met neutrale gezichtsuitdrukkingen suggereert dat het sociale aspect van de stressoren van belang is. In deze studie was het aantal participanten in de ultra high risk groep klein (n = 20), bestond deze vooral uit vrouwen, en rapporteerde deze groep gemiddeld meer psychotische klachten dan de psychosegroep. Dit kan mogelijk worden verklaard doordat deze groep in een eerdere fase van behandeling werden geïncludeerd of omdat ze geen gebruik maakte van anti psychotische medicatie. Dit kan hebben geleid tot een onderschatting van het effect van de psychosegevoeligheid op achterdocht en angst in virtual reality. Cognitieve biases werden gemeten door middel van zelfrapportage en beperkt tot vier cognitieve biases. Ten slotte rapporteerden deelnemers slechts weinig cybersickness en weinig tot geen angstklachten, wat de statistische power beperkte bij deze analyses.

De tweede studie, naar het behandeleffect van in virtual reality gebaseerde cognitieve gedragstherapie, heeft drie belangrijke beperkingen. We hebben geen gebruik gemaakt van een actieve controle conditie, waardoor we geen dosis-effect van therapeutische contacten kunnen uitsluiten. Ten tweede kunnen we nog niets zeggen over de lange termijn effecten van in virtual reality gebaseerde cognitieve gedragstherapie, want de follow-up meting was beperkt tot slechts zes maanden na de baseline meting. Ten slotte is het waarschijnlijk dat een groep patiënten die in aanmerking kwam voor de behandeling niet heeft deelgenomen, omdat ze te angstig waren naar de therapie-locatie af te reizen. Daardoor is onze steekproef bevooroordeeld, omdat veel van de meest achterdochtige en vermijdende patiënten niet hebben kunnen deelnemen.

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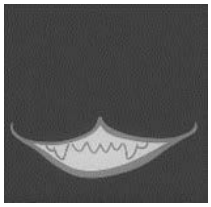

"*I'm not crazy, my reality is just different from yours*"

Cheshire Cat in 'Alice in wonderland' by Lewis Carroll

Toen ik in 2013 als PhD-kandidaat startte had ik niet kunnen bedenken wat een enorm gaaf en totaal uit de hand gelopen avontuur dit zou gaan worden.

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Edwin

Curriculum vitae and publications

Future	I see my future as a clinical-practitioner; combining innovative patientcare and scientific research.
Clinical work	2020 – now: GZ-psychologist & Cognitive Behavioral Therapist at Thubble. 2018 – 2020: GZ-psychologist in training, see 'main education' at Arkin BasisGGZ & Mentrum. 2017 – 2018: Cognitive Behavioral Therapist at Arkin BasisGGZ Amsterdam. Implementing VR-CBT for Paranoia, Social Phobia and Agoraphobia. 2013 – 2016: Part-time psychologist next to my PhD Research at Parnassia Den Haag. Mainly treating Psychosis and comorbid Anxiety Disorders. 2010 – 2013: Psychologist at PsyPoli of the University of Amsterdam (UvA). I worked as a clinical psychologist within research trials. Mainly treating anxiety disorders. 2008 – 2010. Psychologist at PsyQ for several departments: PTSD, Depression and ADHD. 2007: Internship at Parnassia at the Early Intervention Psychosis team.
Main education	April 2018 – September 2020: GZ-Psycholoog (Healthcare Psychologist) April 2018: EMDR 2010 – 2015: 'Cognitive Behavioral Therapist VGCt'. ID VGCt-204328. August 2007: Master Clinical Psychology at Utrecht University
Publications	***English publications:*** https://www.researchgate.net/profile/Roos_Pot-Kolder/research Geraets CNW, Snippe E, van Beilen M, et al. Virtual reality based cognitive behavioral therapy for paranoia: Effects on mental states and the dynamics among them. *Schizophrenia Research* 2020. Pot-Kolder R, Veling W, Geraets C, et al. Cost-Effectiveness of Virtual Reality Cognitive Behavioral Therapy for Psychosis: Health-Economic Evaluation Within a Randomized Controlled Trial. *J Med Internet Res* 2020; **22**(5): e17098. Counotte J, Bergink V, Pot-Kolder R, Drexhage HA, Hoek HW, Veling W. Inflammatory cytokines and growth factors were not associated with psychosis liability or childhood trauma. *PLoS One* 2019; **14**(7): e0219139. Pot-Kolder R, Veling W, Counotte J, van der Gaag M. Anxiety Partially Mediates Cybersickness Symptoms in Immersive Virtual Reality Environments. *Cyberpsychol Behav Soc Netw* 2018; **21**(3): 187-93. Counotte J, Drexhage HA, Wijkhuijs JM, et al. Th17/T regulator cell balance and NK cell numbers in relation to psychosis liability and social stress reactivity. *Brain Behav Immun* 2018; **69**: 408-17. Pot-Kolder RMCA, Geraets CNW, Veling W, et al. Virtual-reality-based cognitive behavioural therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: a single-blind randomised controlled trial. *Lancet Psychiatry* 2018; **5**(3): 217-26. Jongeneel A, Pot-Kolder R, Counotte J, van der Gaag M, Veling W. Self-esteem moderates affective and psychotic responses to social stress in psychosis: A virtual reality study. *Schizophr Res* 2018; **202**: 80-5. Pot-Kolder R, Veling W, Counotte J, van der Gaag M. Self-reported Cognitive Biases Moderate the Associations Between Social Stress and Paranoid Ideation in a Virtual Reality Experimental Study. *Schizophr Bull* 2018; **44**(4): 749-56. Geraets CNW, van Beilen M, Pot-Kolder R, Counotte J, van der Gaag M, Veling W. Social environments and interpersonal distance regulation in psychosis: A virtual reality study. *Schizophr Res* 2018; **192**: 96-101. Counotte J, Pot-Kolder R, van Roon AM, Hoskam O, van der Gaag M, Veling W. High psychosis liability is associated with altered autonomic balance during exposure to Virtual Reality social stressors. *Schizophr Res* 2017; **184**: 14-20. Pot-Kolder R, Veling W, Geraets C, van der Gaag M. Effect of virtual reality exposure therapy on social participation in people with a psychotic disorder (VRETp): study protocol for a randomized controlled trial. *Trials* 2016; **17**(1): 25.

Publications	Veling W, Pot-Kolder R, Counotte J, van Os J, van der Gaag M. Environmental Social Stress, Paranoia and Psychosis Liability: A Virtual Reality Study. *Schizophr Bull* 2016; **42**(6): 1363-71. Veling W, Counotte J, Pot-Kolder R, van Os J, van der Gaag M. Childhood trauma, psychosis liability and social stress reactivity: a virtual reality study. *Psychol Med* 2016; **46**(16): 3339-48. ***Dutch peer reviewed articles:*** Pot-Kolder, R.M.C.A. & Zandee, E. (2015). Virtual Reality Exposure Therapie bij psychose: een casus. *Directieve Therapie*, **35**(1), 5-14. Pot-Kolder, R.M.C.A. (2011). Dit is mijn groep: Omgaan met bloosangst. *Groepen; Tijdschrift voor Groepsdynamica & Groepspsychotherapie*, **6**(4), 41-48. ***Book chapters:*** Pot-Kolder R, van der Gaag M. Exposure therapie in een virtuele omgeving. In A. van Emmerik & A. Greeven. Handboek Exposure: Amsterdam : Boom, 2020: 157-175. Pot-Kolder R, Jongeneel A & Riper H. E-health. In M. van der Gaag & A. Staring (Eds.), Handboek Psychose: Amsterdam : Boom, 2019: 248-255. Van der Gaag M, van der Berg D, Ising H, Pot-Kolder R, Myin-Germeys I. Psychotherapie. In W. Cahn, I. Myin-Germeys, R. Bruggeman & L. de Haan (Eds.), Handboek Schizofreniespectrum-stoornissen: Amsterdam : de Tijdstroom/Boom; 2019: 657-677. Pot-Kolder R, Veling W, Brinkman W-P, van der Gaag M. Virtual Reality and Psychotic Disorders. In A. Rizzo & S. Bouchard (Eds.), Virtual Reality for psychological and Neurocognitive Interventions: New York, NY : Springer New York : Springer; 2019: 289-305.
Teaching	2020 – Lecturer (English) at Universiteit Twente 2020 – Teaching the 'Psychosis' course in the postdoctoral GZ-education 2019 – 2020: Dutch guest lectures at VU University 2017 – 2020: Yearly guest lecture (English) at Leiden University: 'Virtual Reality Therapy' 2010 – 2013: Teaching clinical psychology Master courses at University of Amsterdam (UvA)
Extra	• 2013: Full Scholarship. Cognitive Behavior Therapy for Schizophrenia: A Recovery-Oriented Model. Under the direction of Judith S. Beck, PhD, and led by Aaron Brinen, PsyD and Paul Grant, PhD and Dr. Aaron Beck. At the Beck Institute in Philadelphia. • 2015: Obtained funding. 55,000 Euro 'Stichting tot steun VCVGZ' for one year of academic writing on: multicenter single-blind randomized controlled trial on virtual-reality-based cognitive behavioral therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders. • 2016: Young Talent Keynote 12th Phrenos Psychosecongress. "Virtual reality: a bridge between the therapist office and daily life".

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